VOLUME XXV NUMBER 6

DISEASES

of the

CHEST

OFFICIAL PUBLICATION

PUBLISHED MONTHLY

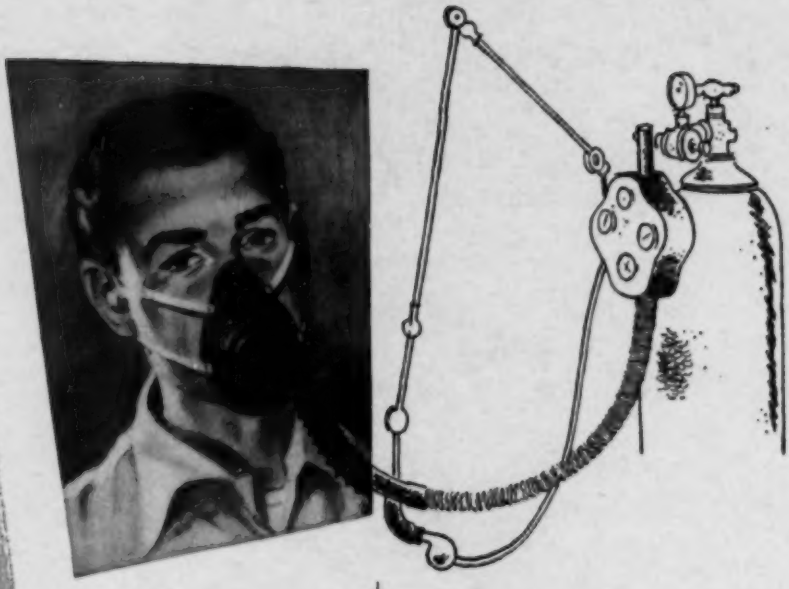
JUNE
1954

INDEX NUMBER

PUBLICATION OFFICE, ALAMOGORDO ROAD, EL PASO, TEXAS
EXECUTIVE OFFICE, 112 EAST CHESTNUT STREET, CHICAGO 11, ILLINOIS

Entered as Second Class Matter August 18, 1936, at the Postoffice at El Paso, Texas
Under the Act of Congress of August 12, 1912.
Copyright, 1954, by the American College of Chest Physicians

Third International Congress on Diseases of the Chest
Barcelona, Spain, October 4-8, 1954



I.P.P.B.

When you order intermittent positive pressure breathing treatments to be given at home for chronic pulmonary disease, your patient can obtain LINDE oxygen U. S. P. from a local distributor.

For the name of the LINDE oxygen distributor in your area, look under "Oxygen" in the classified section of your telephone directory or write to LINDE's Oxygen Therapy Department.

LINDE AIR PRODUCTS COMPANY
A Division of
Union Carbide and Carbon Corporation

UCC

30 East 42nd Street, New York 17, N. Y.
Offices in Principal Cities
In Canada: Dominion Oxygen Company, Limited, Toronto

The term "Linde" is a registered trade-mark of Union Carbide and Carbon Corporation

You are cordially invited to visit our

Booth No. 5

in San Francisco, June 17 - 20.

Viomycin* Sulfate

"a third potent tuberculostatic agent"[1]

now available as **Vinactane**™ **Sulfate**

Viomycin Sulfate Ciba

- Active even when bacillary resistance to streptomycin or isoniazid has developed
- Side effects rare and generally mild in therapeutic dosage
- Especially recommended in combination with PAS

Supplied as sterile vials: The equivalent of 1 Gram viomycin base as the sulfate.

1. Hobby, G. L., Lenert, T. F., Rivoire, Z. C., Donikian, M., and Pikula, D.: Am. Rev. Tuberc. 67:808, 1953.

Detailed literature sent on request of physicians

Ciba Pharmaceutical Products, Inc., Summit, N. J.

*Isolated in Ciba Research Laboratories

9/10040

Ciba

SPECIFY

BIO

VITAMINS

VICAP FORTIOR

BALANCED (Improved) HIGH POTENCY

— For General Therapeutic Use —

A valuable supplement in the regimen of the tuberculosis patient to assist in rectifying deficiencies caused by:

Febrile conditions — Poor Nutrition — Faulty Absorption

Vitamins and Minerals Plus Choline, Inositol and dl-methionine.

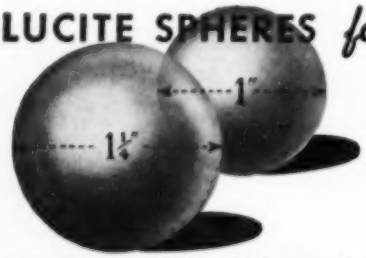
VITAMINS, PER CAPSULE:		MINERALS, PER CAPSULE	
Vitamin A (Synthetic Vitamin Palmitate)	12,500 USP Units	Ca (from DiCalcium Phosphate, Anhydrous)	75 mg.
Vitamin D (Irradiated Ergosterol)	1,000 USP Units	P (from DiCalcium Phosphate, Anhydrous)	58 mg.
Vitamin B-1 (Thiamine Hydrochloride, USP)	5 mg.	Fe (from Ferrous Sulfate, Dried, USP)	30 mg.
Vitamin B-2 (Riboflavin, USP)	2.5 mg.	Cu (from Copper Sulfate, Monohydrate)	0.45 mg.
Vitamin B-6 (Pyridoxine Hydrochloride)	0.5 mg.	Mn (from Manganese Sulfate, Dried)	0.5 mg.
Vitamin B-12, USP	1 microgram	K (from Potassium Sulfate)	2 mg.
Vitamin C (Ascorbic Acid, USP)	75 mg.	Mg (from Magnesium Sulfate, Dried)	3 mg.
Niacin Amide, USP	40 mg.	I (from Potassium Iodide, USP)	0.075 mg.
Calcium Pantothenate	4 mg.	Co (from Cobalt Sulfate)	0.04 mg.
Vitamin E (d-alpha Tocopherol Acetate [from vegetable oils] equivalent by biological assay to 2 I. U. Vitamin E)		Mo (from Sodium Molybdate)	0.1 mg.
Folic Acid, USP	0.5 mg.	Zn (from Zinc Sulfate, Dried)	0.5 mg.

Choline Bitartrate, 31.4 mg. Inositol, 15 mg. dl-Methionine, 10 mg.

Biochemical Research Laboratories, Inc.

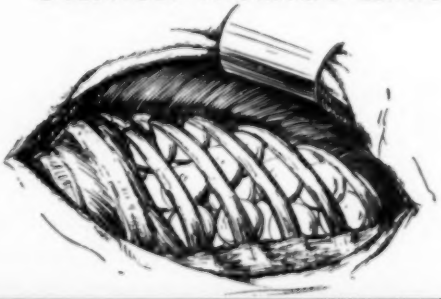
One East Walton Place Chicago 11, Illinois

LUCITE SPHERES *for Plumbage Thoracoplasty*



. . . as used by the

OVERHOLT THORACIC CLINIC



Lucite Spheres, 1¼" or 1" (in diam.) . . . $.30 ea.

Polyethylene Film, Animal Tested, (Used for encasing Spheres)

54" x .015 . . . 10 yds. $7.50

54" x .002 . . . 10 yds. $7.50

ORDER DIRECT FROM:

ESTABLISHED 1830

Codman & Shurtleff, Inc.

MAKERS OF SURGEONS' INSTRUMENTS

104 BROOKLINE AVENUE BOSTON 15, MASSACHUSETTS

DISEASES *of the* CHEST

OFFICIAL PUBLICATION
OF THE
AMERICAN COLLEGE OF CHEST PHYSICIANS

EDITORIAL BOARD

JAY ARTHUR MYERS, M.D., Chairman
Minneapolis, Minnesota
Editor-in-Chief

MILTON W. ANDERSON, M.D.
Rochester, Minnesota

ANDREW L. BANYAI, M.D.
Milwaukee, Wisconsin

RICHARD H. OVERHOLT, M.D.
Brookline, Massachusetts

HENRY C. SWEANY, M.D.
Tampa, Florida

ASSOCIATE EDITORS

ANTONIO A. ADAMES, M.D.	Holtville, California
WILLIAM B. BEAN, M.D.	Iowa City, Iowa
EDWARD P. EGLEE, M.D.	New York, New York
SEYMOUR M. FARBER, M.D.	San Francisco, California
EDWARD W. HAYES, M.D.	Monrovia, California
HANS H. HECHT, M.D.	Salt Lake City, Utah
PAUL H. HOLINGER, M.D.	Chicago, Illinois
CHEVALIER L. JACKSON, M.D.	Philadelphia, Pennsylvania
HOLLIS E. JOHNSON, M.D.	Nashville, Tennessee
ALDO A. LUISADA, M.D.	Chicago, Illinois
ARTHUR M. MASTER, M.D.	New York, New York
EDGAR MAYER, M.D.	New York, New York
ALTON OCHSNER, M.D.	New Orleans, Louisiana
GEORGE G. ORNSTEIN, M.D.	New York, New York
J. WINTHROP PEABODY, M.D.	Washington, D.C.
ARTHUR Q. PENTA, M.D.	Schenectady, New York
LEO G. RIGLER, M.D.	Minneapolis, Minnesota

CORRESPONDING ASSOCIATE EDITORS

Donato G. Alarcon, M.D., Mexico
Adrian Anglin, M.D., Canada
Jose Ignacio Baldo, M.D., Venezuela
Etienne Bernard, M.D., France
Miguel Canizares, M.D., Philippine Is.
Manoel de Abreu, M.D., Brazil
Lopo de Carvalho, M.D., Portugal
Sir Alexander Fleming, M.D., England
Ovidio Garcia Rosell, M.D., Peru
Fernando D. Gomez, M.D., Uruguay
Affonso MacDowell, M.D., Brazil
David P. Marais, M.D., South Africa
Amadeo V. Mastellari, M.D., Panama
Gustav Maurer, M.D., Switzerland
Andre Meyer, M.D., France
Papken S. Mugriditchian, M.D., Lebanon
Antonio Navarrete, M.D., Cuba
Juda M. Pauzner, M.D., Israel
Hector Orrego Puelma, M.D., Chile
Raul F. Vaccarezza, M.D., Argentina
Raman Viswanathan, M.D., India
Harry W. Wunderly, M.D., Australia
Attilio Omodei Zorini, M.D., Italy

EXECUTIVE OFFICE
112 East Chestnut Street, Chicago 11, Illinois
MURRAY KORNFELD, *Managing Editor*

VOLUME XXV JUNE 1954 NUMBER 6

CONTENTS

STREPTOMYCIN SENSITIVITY OF TUBERCLE BACILLI FROM RESECTED LUNGS 601
Eric W. Stern, M.D. and Alfred Goldman, M.D., Los Angeles, California

CLINICAL OBSERVATIONS ON THE USE OF ISONIAZID IN TUBERCULOSIS 611
Howard M. Payne, M.D., Robert L. Hackney, Jr., M.D., Eugene A. Clark, M.D. and Preston C. Johnson, M.D., Washington, D. C.

TREATMENT OF PULMONARY TUBERCULOSIS WITH ISONIAZIDE AND IPRONIAZIDE 622
Samuel Cohen, M.D. and Eriberto Ang, M.D., Jersey City, New Jersey

ALTERNATING POSITIVE-NEGATIVE PRESSURES IN MECHANICAL RESPIRATION 640
(The Cycling Valve Device Employing Air Pressures)
M. S. Segal, M.D., A. Salomon, M.D. and J. A. Herschfus, M.D., Boston, Massachusetts

PULMONARY COMPLICATIONS OF HEART DISEASES 649
N. E. Reich, M.D., Brooklyn, New York

SARCOMA OF THE LUNG 663
Theodore H. Noehren, M.D. and Frank W. McKee, M.D., Buffalo, New York

INTRAABDOMINAL COMPLICATIONS AND SEQUELLAE OF PNEUMOPERITONEUM 679
R. T. Fox, M.D., J. R. Thompson, M.D., O. L. Bettag, M.D., E. S. Gilbert, M.D. and W. M. Lees, M.D., Chicago, Illinois

PNEUMOPERITONEUM THERAPY: SOME CONTRAINDICATIONS; ANATOMY OF OMENTAL BURSA 689
Joseph C. Mulhern, M.D., Sanatorium, Mississippi

CYTOLOGY—A MEANS OF LEARNING DISEASE PROCESSES 696
Seymour M. Farber, M.D., San Francisco, California

KNOWLEDGE IS NOT ENOUGH 698
Alvis E. Greer, M.D., Houston, Texas

THE PRESIDENT'S MESSAGE 701
Alvis E. Greer, M.D., Houston, Texas

OBITUARY: Herbert L. Mantz, 1896-1953 703

AUTHOR INDEX, January-June, 1954 705

SUBJECT INDEX, January-June, 1954 712

CONTENTS, Volume XXV, January-June, 1954 715

MEDICAL SERVICE BUREAU xxi

CALENDAR OF EVENTS xxii

Entered as second class matter, August 18, 1936, at the postoffice at El Paso, Tex., under the Act of August 24, 1912

Annual Subscription: $12.50, Postpaid to any part of the World.

ANNOUNCING

GANTRICILLIN-300

GANTRISIN + PENICILLIN

IN A SINGLE TABLET

GANTRICILLIN-300 provides 300,000 units of penicillin plus 0.5 Gm of Gantrisin, the single, highly soluble sulfonamide. Especially useful in conditions in which the causative organisms are more susceptible to the combination than to either Gantrisin or penicillin alone.

Gantrisin 'Roche' "would seem to be an ideal sulfonamide to use where it is desirable to combine sulfonamide administration with other antibacterial agents."

Herrold, R. D.: Surg. Clin. North America 30:61, 1950.

Also available—Gantricillin (100), containing 0.5 Gm Gantrisin and 100,000 units of crystalline penicillin G potassium.

Supplied: Bottles of 24, 100 and 500 tablets.

Gantricillin® Gantrisin®—brand of sulfisoxazole (3,4-dimethyl-5-sulfanilamido-isoxazole)

HOFFMANN-LA ROCHE INC • ROCHE PARK • NUTLEY 10 • N. J.

MEDICAL BOOK SERVICE DEPARTMENT

American College of Chest Physicians

POSTAGE PREPAID TO ANY PART OF THE WORLD

THE CHEST AND THE HEART, J. A. Myers, M.D. and C. A. McKinlay, M.D. and associates; 2 volumes; 1856 pages; 1003 illustrations	$25.50
TUBERCULOSIS AS IT COMES AND GOES, Edward W. Hayes, M.D.; 228 pages; 96 illustrations	4.50
RADIATION AND CLIMATIC THERAPY OF CHRONIC PULMONARY DISEASES, INCLUDING ALL FORMS OF TUBERCULOSIS, Edited by Edgar Mayer, M.D.; 406 pages; 46 figures	5.00
DISEASES OF THE CHEST, Eli H. Rubin, M.D.; 685 pages; 355 figures	14.50
PNEUMOPERITONEUM TREATMENT, A. L. Banyai, M.D.; 376 pages; 74 illustrations	7.50
X-RAY DIAGNOSIS OF CHEST DISEASES, Coleman B. Robia, M.D., 208 pages, 373 illustrations	12.00
ARTIFICIAL PNEUMOTHORAX IN PULMONARY TUBERCULOSIS, T. G. Heaton, M.D.; 292 pages	4.50
SURGICAL EXTRAPLEURAL PNEUMOTHORAX, Donato G. Alarcon, M.D.; 298 pages	8.00
THE TECHNIQUE OF PULMONARY RESECTION, R. H. Overholt, M.D. and L. Langer, M.D.; 224 pages; 122 illustrations	8.00
THE FUNDAMENTALS OF PULMONARY TUBERCULOSIS AND ITS COMPLICATIONS, Sponsored by the American College of Chest Physicians; 492 pages; 219 illustrations	9.50
THE MANAGEMENT OF THE PATIENT WITH SEVERE BRONCHIAL ASTHMA, Maurice S. Segal, M.D.; 168 pages; 24 illustrations	3.50
SECTIONAL RADIOGRAPHY OF THE CHEST, Irving J. Kane, M.D., 164 pages, 243 illustrations	7.50
RADIOLOGIC EXPLORATION OF THE BRONCHUS, S. De Rienzo, M.D.; 348 pages; 520 illustrations	10.75
CYTOLOGIC DIAGNOSIS OF LUNG CANCER, S. M. Farber, M.D., et al.; 90 pages; 60 full color illustrations	6.00
BRONCHIAL ASTHMA, Leon Unger, M.D.; 740 pages; 202 illustrations	10.50
PHYSIOLOGIC THERAPY IN RESPIRATORY DISEASES, Alvan L. Barach, M.D.; 408 pages; 74 illustrations	9.00
BRONCHOESOPHAGOLOGY, Chevalier Jackson, M.D. and Chevalier L. Jackson, M.D.; 366 pages; 260 illustrations	13.00
THE UNCOMMON HEART DISEASES, Nathaniel E. Reich, M.D., 516 pages, numerous illustrations	10.50

The above is a partial listing of medical books available through the Medical Book Service Department.

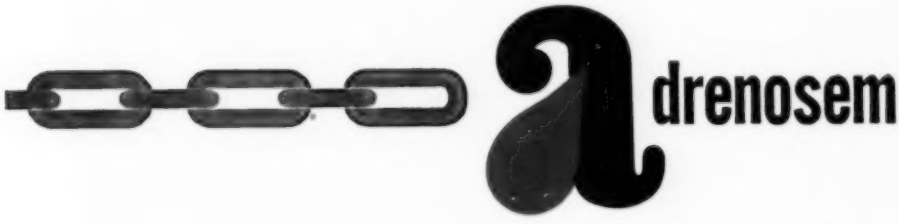
Please send your order to:
MEDICAL BOOK SERVICE DEPARTMENT,
American College of Chest Physicians
112 East Chestnut Street, Chicago 11, Illinois

"where oozing from a vascular bed is anticipated"*

ADRENOSEM stops capillary bleeding and oozing. Adrenosem acts directly on the capillary walls to increase resistance and decrease permeability.

There are no reported toxic effects or contraindications attributable to Adrenosem. Adrenosem does not affect blood components or induce embolus formation. It has no sympathomimetic or vasoconstrictive action. Adrenosem is compatible with vitamin K, heparin, and commonly used anesthetics. (It is suggested, however, that antihistamines be withheld for 48 hours prior to and during Adrenosem therapy since antihistamines tend to inactivate Adrenosem.)

*Sherber, D. A.: The Control of Bleeding. Am. J. Surg. *86*:331 (Sept.) 1953.



the missing link in the control of bleeding

The therapeutic regimen for Adrenosem is *simple* and *safe:*

- *preoperatively* to control oozing during surgery and provide clearer operative field: one to two ampuls (5 to 10 mg.) every two hours prior to surgery for two doses.
- *postoperatively* to prevent hemorrhage and check oozing: one to two ampuls (5 to 10 mg.) every two hours until there is no indication of undue bleeding. To maintain control, one ampul may be administered every three hours or 1 to 5 mg. orally t. i. d.
- to control *active bleeding:* One ampul (5 mg. every two hours until bleeding is controlled; frequency of dose may then be diminished.
- to control *severe bleeding:* one ampul (5 mg.) every hour for three doses; then every three hours until bleeding is controlled.
- to control *mild, low-grade bleeding:* 1 ampul (5 mg.) every three or four hours until bleeding is controlled; then 1 to 5 mg. orally four to five times daily until bleeding ceases.
- *maintenance dosage* to prevent bleeding in conditions where small vessel integrity may be impaired: 1 to 5 mg. orally t. i.d.; if bleeding ensues, dosage may be increased 1 to 5 mg. orally every three or four hours; if bleeding persists, oral dosage should be supplemented with 1 ampul (5 mg.) daily.
- *pediatric dosage:* up to four years of age – 1 mg. intramuscularly or orally with same frequency as for adults, until bleeding is controlled. From four to twelve years of age – ½ the adult dosage as indicated.

Available as Ampuls: 5 mg., 1 cc. (package of 5).
Tablets: 1 mg. S. C. Orange, bottles of 50.
Tablets: 2.5 mg. S. C. Yellow, bottles of 50.

SE M CO

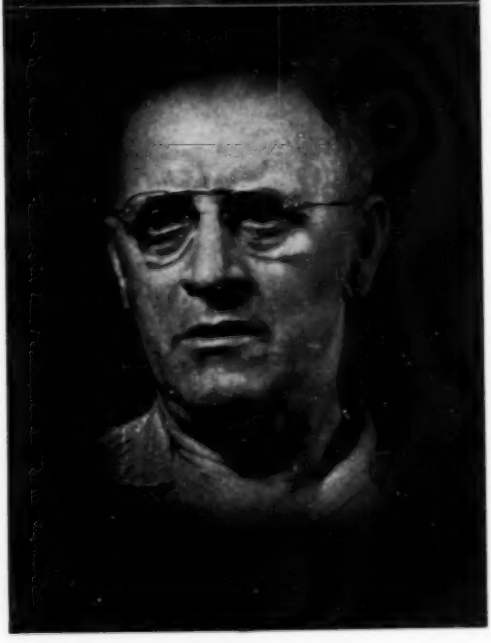
THE S. E. MASSENGILL COMPANY, Bristol, Tennessee
New York • San Francisco • Kansas City

Adrenosem – Massengill Brand of Adrenochrome Semicarbazone Sodium Salicylate Compound

Dexamyl* helped...

. . . Patient S.B.,
an osteoarthritic, through
long weary weeks of diathermia,
infrared treatments,
and wearing a brace.

. . . Patient S.H.,
who complained of precordial
uneasiness, chronic fatigue,
and apprehension about his
work and ill wife.



(case reports of a general practitioner; unposed photographs taken during office visit)

★T.M. Reg. U.S. Pat. Off.

When writing please mention *Diseases of the Chest*

"This patient was under my direct and constant care for 8 months. . . . After the first week's medication ['Dexamyl'] her mood was greatly improved. . . . When the brace gave her physical relief, we were able to reduce the dosage. She herself discontinued 'Dexamyl' after the sixth month—except before her period."

'Dexamyl' provides the synergistic action of *two* mood-ameliorating components:

Tablets—each containing Dexedrine* Sulfate (dextro-amphetamine sulfate, S.K.F.), 5 mg.; amobarbital, ½ gr. (32 mg.).

Elixir—each teaspoonful (5 cc.) equivalent to one tablet.

"Three factors contributed to this man's recovery: (1) I had his wife successfully operated upon, (2) both of them took a much needed vacation, and (3) I prescribed 'Dexamyl' when he returned to work. . . . His days became smooth and his nights smoother. . . . After 3 months he was able to reduce the dosage considerably . . . he was able to work better, view his problems more objectively, and slept well. As he expressed it, 'If my day goes well, the night will take care of itself.' "

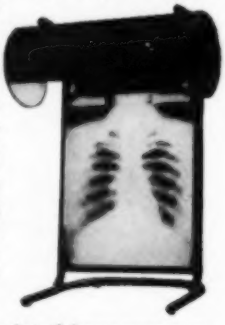
'Dexamyl' tablets and elixir

relieves both anxiety and depression
promotes a feeling of composure

Smith, Kline & French Laboratories
Philadelphia

POWERS X-RAY PAPER REDUCES COSTS 50% OR MORE!

For most routine work, radiographs of high quality can be made at less than half the usual cost with Powers X-Ray Paper. That is why more and more hospitals are using *both* paper and celluloid base film in their X-Ray departments. Techniques differ only slightly.



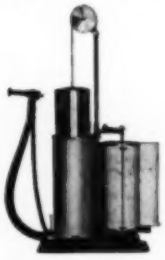
Proven in use for over 16 years, Powers X-Ray Paper comes in standard sheet sizes, or perforated rolls for use with the Powers Magazine Cassette.

Let us show you in detail how you can effect substantial savings with Powers X-Ray Paper. Write for complete information and literature.

POWERS X-RAY PRODUCTS, INC.

Reg. U. S. Pat. Off.
POWERS X-RAY PRODUCTS
Group Radiography
Glen Cove, Long Island, N. Y.

FOR CARDIORESPIRATORY FUNCTION TESTS



The COLLINS RESPIROMETER

The Respirometer is used in the measurement of the following static and dynamic pulmonary volumes:

- TIDAL VOLUME
- MINUTE VOLUME
- VITAL CAPACITY
- MAXIMUM BREATHING
- OXYGEN DEFICIT
- MINUTE O_2 UPTAKE
- FUNCTIONAL RESIDUAL CAPACITY
- RESIDUAL VOLUME
- CONSTANT GAS AND ROOM AIR BREATHING
- BRONCHOSPIROMETRY

3 REPRINTS ON BRONCHOSPIROMETRY

by a leading authority entitled III Complications, Contraindications, Technique and Interpretation: IV Ambient-Air and Oxygen—Recording Bronchospirometry: and V Differential Residual Volume Determination are available for the asking. Just mail the Coupon NOW.

WARREN E. COLLINS, INC.
555 HUNTINGTON AVENUE,
BOSTON 15, MASSACHUSETTS

Please send me the 3 Bronchospirometry reprints and information on

( ) Respirometer ( ) "Timed" Vital ( ) Broncho-spirometer
( ) Chain Compensated Gasometer

Signed _____
Street _____
City _____ Zone _____
State _____ DC-6

The American College of Chest Physicians
presents a *new* book

NONTUBERCULOUS DISEASES *of the* CHEST

Sponsored by the
American College of Chest Physicians

Editor
ANDREW L. BANYAI, M.D.

Editorial Committee
Seymour M. Farber, M.D.
Alvis E. Greer, M.D.
Charles M. Hendricks, M.D.
Minas Joannides, M.D.
J. Arthur Myers, M.D.
George G. Ornstein, M.D.
J. Winthrop Peabody, M.D.

This is a companion volume to
FUNDAMENTALS OF PULMONARY TUBERCULOSIS AND ITS COMPLICATIONS
also published by
Charles C Thomas • *Publisher*
and sponsored by the
American College of Chest Physicians

1113 pages (6¼ x 9½)
255 illustrations

$18.75, postpaid

This volume offers to the practicing physician, the chest specialist and to students of medicine, up-to-date, competent information relative to the manifold questions in the field of chest diseases—and is important at this time because these diseases (nontuberculous morbid conditions of the lung, pleura, esophagus and other structures of the chest) represent an important, often grave, problem clinically as well as individually and socially and they are taking a tremendous toll of human lives throughout the world.

This book presents the essence of the vast clinical experience of men who devote their time to the practice of teaching this specialty.

Thirty-seven contributors from the United States, Argentina, England, India, and Mexico assure an encompassing, precise and modern presentation of data concerning the multitude of diseases of the chest.

In addition to a critical review of available diagnostic procedures, new methods are offered for the management of various clinical entities.

Special chapter on: INDUSTRIAL DISEASES OF THE LUNG—a discussion of industrial hazards and the assaying of lung diseases caused by exposure to noxious fumes, gases, and dusts. Valuable data are included on the estimation of disability in and the prevention of pneumoconiosis.

The pathology, symptomatology, diagnosis and treatment of FOREIGN BODIES IN THE AIR AND FOOD PASSAGES are covered in a well illustrated chapter.

Mail Your Order Today
American College of Chest Physicians
Medical Book Service Dept.
112 East Chestnut Street
Chicago 11, Illinois

Please send one copy of *Nontuberculous Diseases of the Chest*. Enclosed is my check for $18.75.

NAME .....

ADDRESS .....

CITY ..... STATE .....

Continuous

Aerosol-Oxygen Therapy

FOR
- COLD MIST NEBULIZERS
- OPEN TOP TENTS
- TRACH O_2 MIST UNITS

Mist O_2 Gen

- ADAPTABLE
- PORTABLE
- DEPENDABLE

MIST O_2 GEN EQUIPMENT CO.

2711 ADELINE STREET • OAKLAND 7, CALIFORNIA

Equipment available only on order of a physician or a qualified hospital.

B A R C E L O N A . . . .

One of the Most Beautiful Cities in the World

invites you to the

THIRD INTERNATIONAL CONGRESS ON

DISEASES OF THE CHEST

sponsored by the

AMERICAN COLLEGE OF CHEST PHYSICIANS

COUNCIL ON INTERNATIONAL AFFAIRS

Barcelona, Spain, October 4 - 8, 1954

XIII CONFERENCE, INTERNATIONAL UNION AGAINST TUBERCULOSIS

M A D R I D , S P A I N

September 26 - October 2, 1954

When writing please mention *Diseases of the Chest*

Meltzer Nasopharyngoscope

CALIBRE—7 Fr.

VISUAL FIELD—large, sharply defined, high contrast

Accurate, detailed inspection of the smallest cavities and canals of the nasopharyngeal region is now possible with the Meltzer Nasopharyngoscope. Its minute calibre permits its use between the middle turbinate and septum to explore the superior meatus and sphenoethmoidal regions. It can be used under the middle turbinate to study the accessory ostium and the bulla ethmoidalis and openings of the ethmoidal cells can be seen.

Its coated lens system and cartridge type lamp produce a brilliantly illuminated, sharply defined image. The superior optical properties characteristic of A.C.M.I. telescopes are retained in the Meltzer Nasopharyngoscope. The cartridge type lamp located adjacent to the objective lens assures maximum illumination. Coated lens system provides a large visual field, sharply defined and free from internal reflections. A protective sheath that may be used as a sterilizing chamber is supplied with the instrument.

Cat. No. 586

American Cystoscope Makers, Inc.

1241 LAFAYETTE AVE. FREDERICK J. WALLACE, President NEW YORK 59, N. Y.

Send it in today

Irwin, Neisler & Company
Decatur, Illinois

Please send me, without cost or obligation, the new asthma kit containing Dylephrin, Cardalin and Dainite for my personal clinical evaluation.

_____ M. D.

_____ STREET

CITY _____ STATE _____

for your Personal

CLINICAL EVALUATION

This compact asthma kit containing Dylephrin, Cardalin and Dainite is yours, upon request, without charge or obligation. Since dramatic relief is afforded with small doses, each kit contains enough medicament for treatment of 10 patients. Complete clinical data and bibliography enclosed.

FOR FLEXIBLE MANAGEMENT OF THE ASTHMATIC PATIENT

a preparation for every need...

NEW DYLEPHRIN aerosol

NEW . . . dual bronchodilator aerosol markedly increases vital capacity in the asthmatic patient

Dylephrin is the first available aerosol solution of epinephrine and atropine that is *stable* and will maintain its therapeutic potency. Dylephrin combines the potent action of these two drugs to produce a rapid and far greater increase in the vital capacity of the asthmatic than is possible with epinephrine alone.

Dylephrin's dramatic antiasthmatic action is not marred by side effects. In an extensive study, all patients who used Dylephrin preferred it to any other preparation they used before.

aerosol	no. of cases	Vital Capacity (mean % increase over control)
Dylephrin	27	+27.0
racemic epinephrine	30	+18.3
placebo	12	− 0.2

Beck, G. V., Bickerman, H. A., and Marder, M. J.: to be published.

MORE PRONOUNCED RELIEF

CARDALIN tablets

for truly therapeutic theophylline blood levels higher and better sustained than with I.V. aminophylline

Cardalin provides 5 gr. of aminophylline per tablet—the highest concentration for oral use—*plus* two protective factors that effectively counteract gastric irritation. With Cardalin, increases in mean vital capacity and maximum breathing capacity are highly significant.

DAINITE® tablets

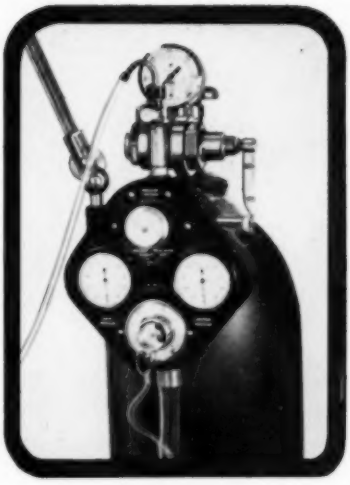
for round-the-clock protection of the asthmatic patient

Dainite Tablets employ the Cardalin principle of protected aminophylline in two distinct dosage forms for the different requirements of day and night. Continuous protection against bronchospasm follows Dainite therapy.

IRWIN, NEISLER & COMPANY · DECATUR, ILLINOIS

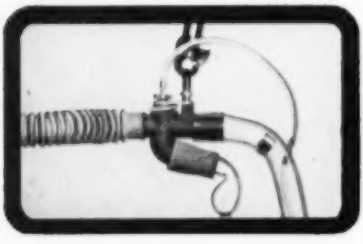
for treatment of acute and chronic pulmonary disorders ... in office, hospital or home

BENNETT PRESSURE BREATHING UNIT (for I.P.P.B.-Insp.) MODEL TV-2P



Current medical researches provide abundant evidence that a considerable percentage of chronic pulmonary impairment is caused by disturbed pulmonary physiology rather than by organic disease. The disturbed function may be in the form of obstruction of the airways and impaired breathing mechanics.

The Bennett Model TV-2P Pressure Breathing Unit has proven to be a major factor among the successful techniques for treatment of these impairments. Intermittent Positive Pressure Breathing (IPPB) combined with simultaneous administration of bronchodilator drugs or antibiotic aerosols is provided by the unit.



MODEL TV-2P

PRICE $340.00

(FOB Los Angeles, Calif.) including *ALL* accessories: Mask, Nebulizer, Flex Tube, Harness, Test Lung, Screw Driver, Cleaning Brush and Instruction Manual.

PRICE $330.00

(FOB Los Angeles, Calif.) when equipped with Mouthpiece and Nose Clip in place of regular Mask and Harness. All other accessories, etc., included.

Convenient carrying case for complete unit optional at $27.50.

Complete new catalog and reprints available on request

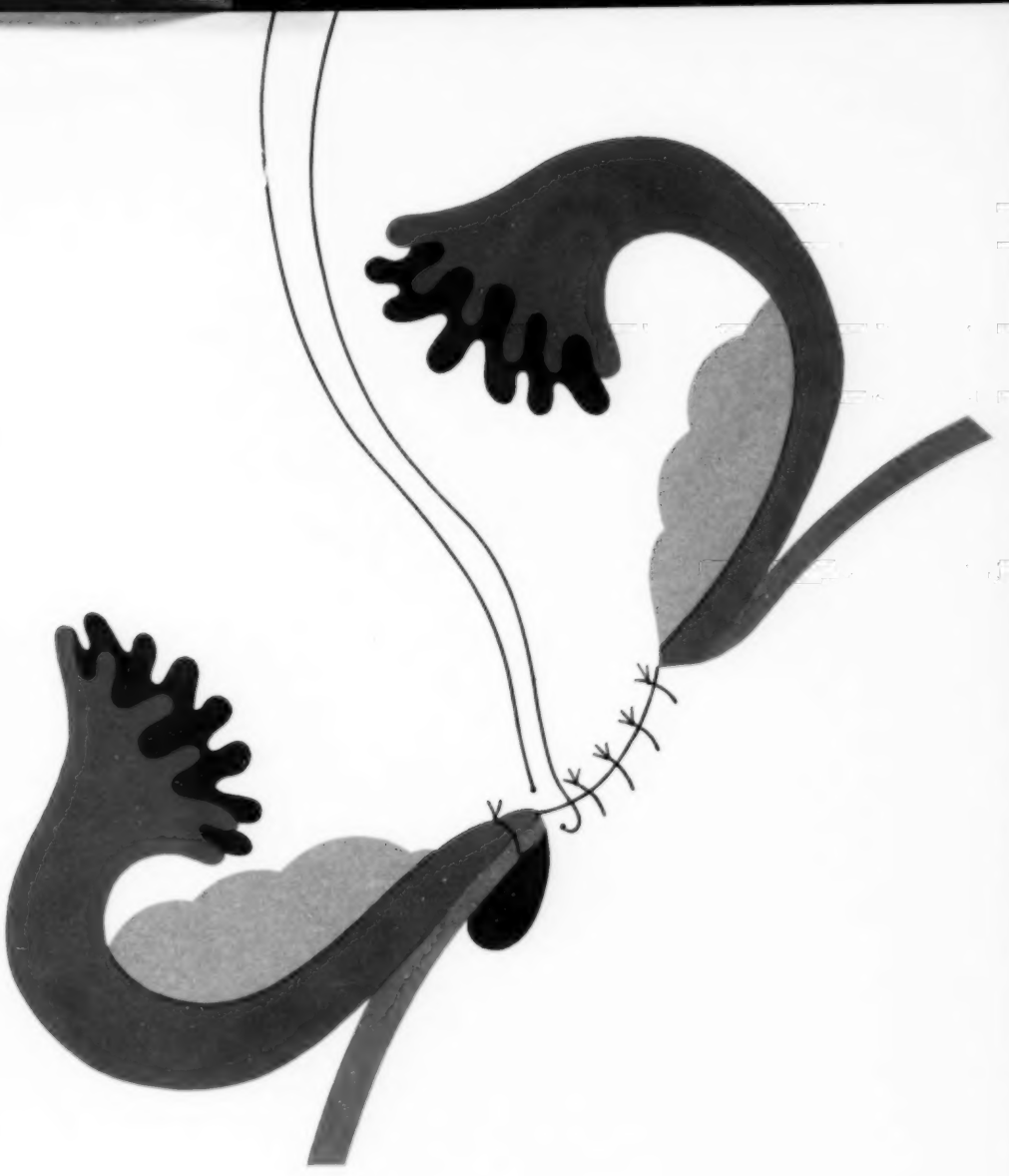
Accepted for Advertising in Journal of American Medical Association

V. RAY BENNETT & ASSOCIATES, INC.

320 S. Robertson Boulevard, Los Angeles 48, Calif.

Units sold only on prescription or order of a physician or qualified hospital or institution.

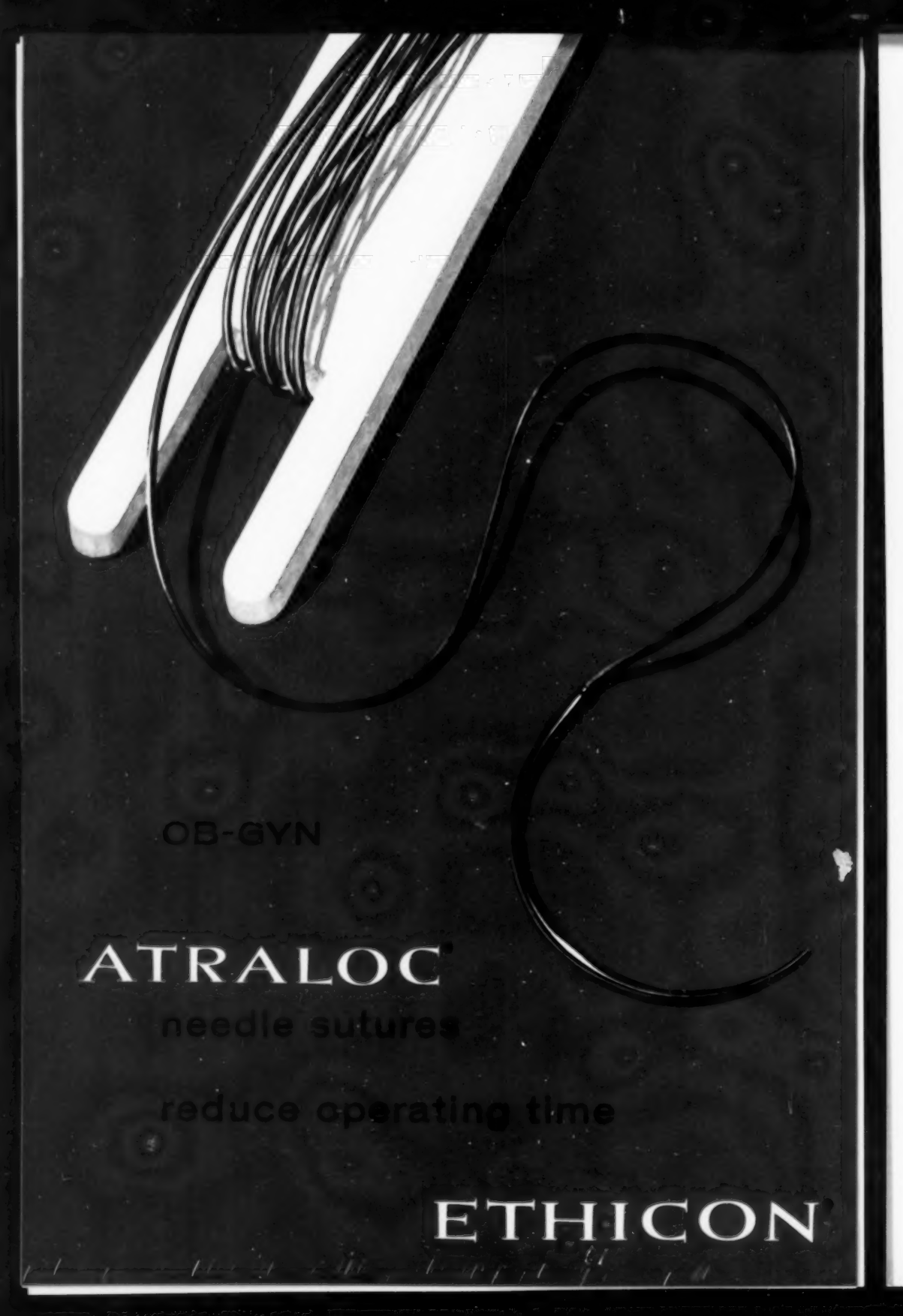
When writing please mention *Diseases of the Chest*

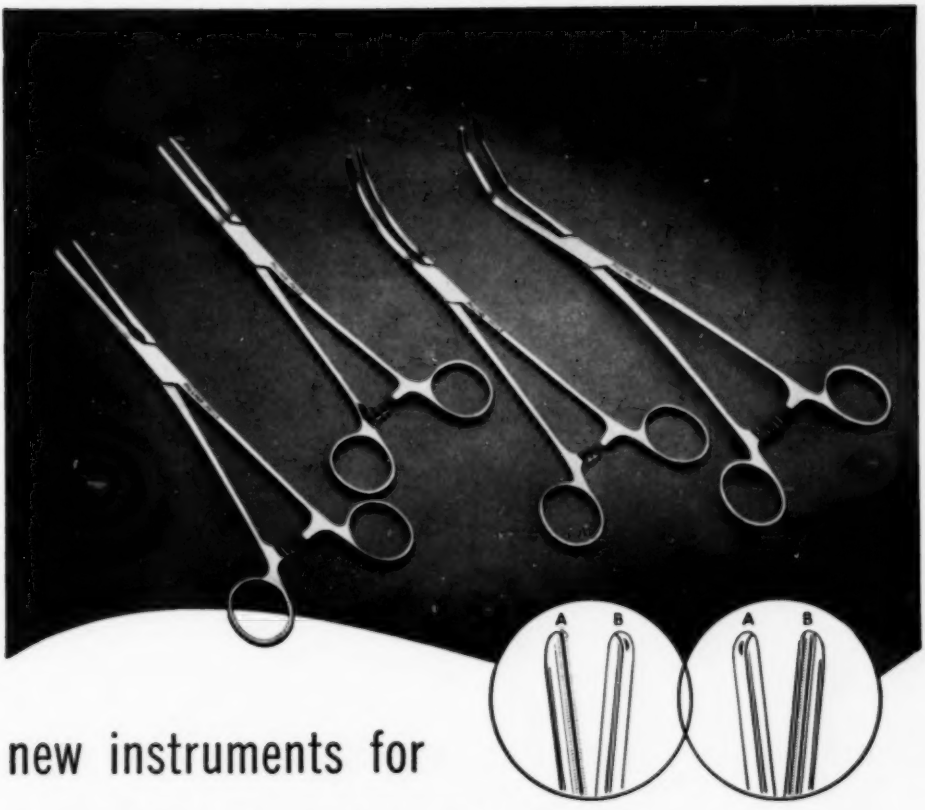


setting new standards

ETHICON®

sutures


OB-GYN
ATRALOC
needle sutures
reduce operating time
ETHICON



new instruments for

Cardiac Surgery with non-traumatic ATRAUGRIP jaws*

Now the cardiac surgeon has the working advantages of fine, perfectly balanced Pilling-made instruments plus the new, noncutting, non-traumatic ATRAUGRIP jaws.

Two rows of finely serrated teeth on one blade and one row on the other, each set in a separate parallel plane, provide a grip which will not slip despite high intravascular pressures or intricate operative procedures. The surgeon is assured a firm grasp of tissue or complete occlusion of blood vessels without danger of crushed or perforated vascular walls or damage to intimal linings.

Write Pilling for data on other instruments for cardiac surgery.

GLOVER AURICULAR APPENDAGE CLAMP
Th2089

GLOVER COARCTATION CLAMP
Th2251 straight
Th2256 angular
Th2275 curved

GLOVER PATENT DUCTUS CLAMP
Th2261 straight
Th2266 angular

*Pat. No. 2668538

THE AUTHENTIC INSTRUMENT IS AVAILABLE ONLY FROM PILLING—ORDER DIRECT:

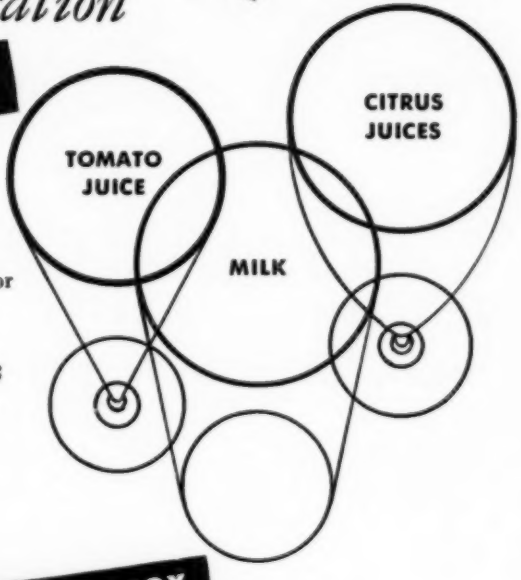
GEORGE P. Pilling & SON CO.

3451 WALNUT STREET, PHILADELPHIA

In Tuberculosis Therapy Choose The Most Versatile- Most Convenient- Most Accurate Method of PAS Administration

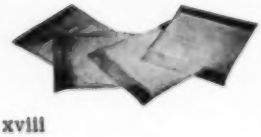
Hellwig's PACKETTES

With Hellwig's PACKETTES the preparation of a single dose of P.A.S. no longer entails measuring powder or counting tablets. No chance of inaccuracy. Each envelope is pre-weighed. Each PACKETTE contains 4.18 grams of *neutral* Sodium Para amino Salicylate Dihydrate (4.18 grams being equal to exactly 3.0 grams of *free* Para amino Salicylic Acid).



50 PACKETTES IN A BOX

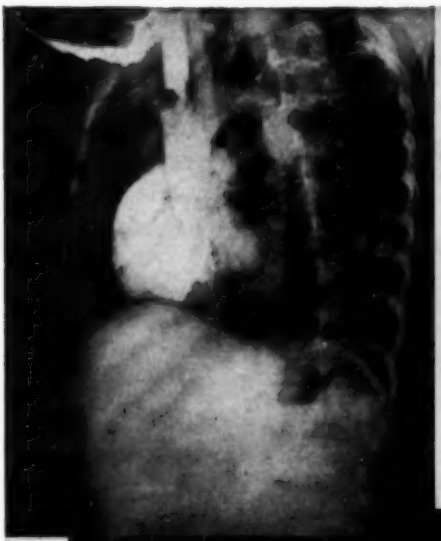
Also available in Junior Size for Children —



Hellwig, Inc.

209 E. Chestnut St.
Chicago, Illinois
Saranac Lake, N. Y.

When writing please mention *Diseases of the Chest*



Angiocardiography

Angiocardiography with Diodrast 70 per cent solution — whether by means of intravenous injection or by the technic of intracardiac catheterization — is now a well standardized and often immensely helpful procedure.

Diodrast

Concentrated Solution 70%

Ampuls of 20 cc. and 50 cc.

Specific instances in which it may be of unsurpassed diagnostic value are congenital lesions such as patent ductus arteriosus, tetralogy of Fallot, coarctation of the aorta, patent foramen ovale, dextrocardia, etc.; aneurysms, mediastinal lesions and chronic pericarditis.

Winthrop Stearns INC.
NEW YORK 18, N. Y. WINDSOR, ONT.

Diodrast, trademark reg. U. S. & Canada, brand of iodopyracet

The M·S·A PULMONARY VENTILATOR...

for better management of EMPHYSEMA

Physicians find this modern instrument extremely effective for treating patients suffering from Emphysema. The instrument's intermittent positive pressure, in conjunction with broncho-dilator drugs, assists in overcoming dyspnea for longer periods.

Equally effective in Asthma, Silicosis and similar diseases, this unit is a welcome aid in the relief of bronchospasm.

You'll find complete facts on design, operation and application in our bulletin. Write for a copy. Price of the M.S.A. Pulmonary Ventilator with mouthpiece assembly and Nebulizer attachment—$195.00.

MSA
SAFETY EQUIPMENT HEADQUARTERS

MINE SAFETY APPLIANCES CO.

Braddock, Thomas and Meade Streets
Pittsburgh 8, Pa.

At Your Service: 82 Branch Offices in the United States and Canada

When writing please mention *Diseases of the Chest*

DISEASES *of the* CHEST

VOLUME XXV JUNE 1954 NUMBER 6

Streptomycin Sensitivity of Tubercle Bacilli from Resected Lungs*

ERIC W. STERN, M.D. and ALFRED GOLDMAN, M.D., F.C.C.P.
Los Angeles, California

Introduction

The development of resistance of tubercle bacilli to streptomycin has been investigated by many workers (Pyle,[1] Steenken,[2] Yegian and Vanderlinde,[3] Minutes of Sixth Streptomycin Conference,[4] Karlson and Needham,[5] Wolinsky, Reginster and Steenken,[6] Bailey[7]). It is believed by most that either a true mutation is caused by the direct action of the drug on the tubercle bacillus or that selection is involved, i.e., that streptomycin resistant mutations are originally present and emerge from among a predominantly sensitive population of bacilli.

The purpose of the present study was to investigate the possible role of the inflammatory reactions of the tissues in producing resistance to streptomycin, since bacteria can change in virulence and in other biologic characteristics when they infect human or animal tissues. Saenz and Canetti[8] reported considerable variation in streptomycin sensitivity of tubercle bacilli in 10 different tuberculous lesions from three autopsies. It appeared to us that surgically resected tuberculous lungs were more suitable material for such a study, because the lesions are more sharply defined in such material and are uncontaminated by terminal spread. Many different kinds and stages of inflammatory reactions are usually present in one and the same specimen, with all other factors constant.

Under aseptic conditions pieces of tissue were removed from several different lesions in each surgical specimen, using a different set of instruments for each piece, and exercising great care in the selection and removal of the tissue to prevent contamination. Tubercle bacilli were then cultured from these tissues and their streptomycin sensitivity was determined.

Preliminary Studies

A large amount of preliminary work was done over a two-year period consisting of a study of changes in streptomycin sensitivity of tubercle

*From the Department of Thoracic Surgery, and Department of Laboratories, City of Hope Medical Center, Duarte, California.

We wish to acknowledge the aid and assistance of Perry Melnick, M.D., former pathologist, City of Hope Medical Center, Duarte, California.

Copyright, 1954, by the American College of Chest Physicians

bacilli obtained at periodic intervals from sputa and gastric washings from 258 patients with chronic pulmonary tuberculosis, the majority of whom were treated with this drug. A total of 834 samples of sputum and gastric washings were cultured in duplicate on Wallenstein's inspissated egg yolk medium. Sub-cultures in duplicate were then made from each culture on American Trudeau Society (ATS) medium (Bailey[7]), which is essentially Herrold's egg yolk agar with 2 per cent malachite green added. Six sets of media were inoculated in duplicate from each culture, each set containing 1, 5, 10, 20, 100, and 1,000 micrograms of streptomycin, respectively, per ml. of media. The technique is the same as that used by most workers in this field and is described by Karlson and Needham.[5] The organisms were then classified as very sensitive, sensitive, resistant or completely resistant, depending on which concentration of streptomycin inhibited their growth. Since the most effective therapeutic blood levels of streptomycin are between 5 and 15 micrograms per ml., 10 micrograms has been widely accepted as the borderline between sensitivity and resistance.

TABLE I: STREPTOMYCIN RESISTANCE OF TUBERCLE BACILLI CORRELATED WITH TOTAL DOSAGE

Total Dosage of Streptomycin (in Grams)	0	30	30-60	60-90
Number of Cases	43	22	26	32
Very Sensitive (VS)	33 (77%)	10 (45.5%)	6 (23.1%)	7 (21.9%)
Sensitive (S)	10 (23%)	12 (54.5%)	12 (46.2%)	11 (34.4%)
Resistant (R)	0	0	8 (30.7%)	14 (43.7%)
Completely Resistant (CR)	0	0	0	0

TABLE I (Continued)

Total Dosage of Streptomycin (in Grams)	90-120	120-200	200 plus
Number of Cases	15	15	3
Very Sensitive (VS)	2 (13.3%)	2 (13.3%)	0
Sensitive (S)	5 (33.3%)	4 (26.7%)	0
Resistant (R)	5 (33.3%)	6 (40%)	0
Completely Resistant (CR)	3 (20%)	3 (20%)	3 (100%)

The results are summarized in Table I. The development of streptomycin resistance is found to be almost directly proportional to the total amount of drug administered. With a total of more than 200 grams all the organisms became completely resistant. These results are in agreement with the work of Pyle,[1] Steenken,[2] Yegian and Vanderlinde,[3] Karlson and Needham,[5] Wolinsky, Reginster and Steenken,[6] and with the experience of the Veterans Administration Hospitals which have been engaged in the streptomycin evaluation program as reported in the minutes of their Sixth Streptomycin Conference.[4]

A second group of 77 patients who received para-aminosalicylic acid, generally combined with streptomycin was also studied. The results are summarized in Table II. Streptomycin resistance was substantially delayed and diminished by combined treatment with PAS. These results are also in complete agreement with the work of Delaude,[9] Karlson et al.,[10] Lehman and Needham,[11] Bloch, Vennesland and Ebert,[12,13] and Dunner, Brown and Wallace.[14] The above preliminary work involved the examination of more than 8,000 individual cultures; reliable and reproducible results could always be obtained with ease.

Histopathologic Correlation

One hundred twenty four specimens were then obtained from 33 patients who had pneumonectomy, lobectomy, or other surgical procedures performed such as cavernostomy or pleural drainage. Tubercle bacilli were cultured from the tissues as well as from sputum and gastric sediment collected a day or two previous to the operation and their streptomycin sensitivity was determined. At the same time the histologic pattern of most of these lesions was correlated with the streptomycin sensitivity of the organisms obtained from them and from the sputum and gastric sediment.

The results were unexpected and are summarized in Table III. It is interesting to note that in each individual case the tubercle bacilli cultured from the different kinds of lesions, whether cavitary, caseous, cellular, fibrotic, or fibro-calcific, as well as from sputum, gastric sediment, or pleural fluid, obtained at the same time all had either exactly the same or very much the same degree of sensitivity to streptomycin. It must be concluded, therefore, that the differences in the inflammatory reactions found in tuberculous lungs are not a factor in the development of streptomycin resistance of tubercle bacilli. Recently Medlar, Bernstein and Reeves[15] reported a study of 95 necropsy specimens from 15 cases of pulmonary tuberculosis which they analyzed in much the same manner as

TABLE II: DELAYED EMERGENCE OF STREPTOMYCIN-RESISTANT TUBERCLE BACILLI ON COMBINED STREPTOMYCIN AND PAS THERAPY

	STREPTOMYCIN ONLY (Control) (60-120 Grams)	STREPTOMYCIN Plus PAS (60-120 Grams)	(720-1440 Grams)
Sensitive	25 (53 per cent)	27 (90 per cent)	
Resistant	22 (47 per cent)	3 (10 per cent)	

TABLE III: STREPTOMYCIN RESISTANCE OF TUBERCLE BACILLI FROM SURGICAL SPECIMENS

CASE NO.	PATIENT	DATE	STREPTOMYCIN	PAS	MATERIAL	RESULTS
(1)	C.R.	5/18/49	170	0	1. Cavernostomy drainage 2. Sputum 3. Gastric	6S; 6R R R
(2)	M.C.	5/20/49	53	0	1. Cavity aspiration 2. Sputum 3. Gastric	S R R
(3)	L.S.	6/28/49	30	0	1. Cavity aspiration 2. Sputum 3. Gastric	VS S S
(4)	J.D.	6/28/49	120	0	1. Cavernostomy drainage 2. Sputum 3. Gastric	CR CR CR
(5)	A.S.	7/17/49	75	0	1. Empyema drainage 2. Sputum 3. Gastric	VS S S
(6)	A.G.	7/17/49	90	0	1. Empyema drainage 2. Sputum 3. Gastric	S S S
(7)	D.G. (LAS-126)	8/ 3 /49	98	0	1. Pneumonectomy: Cavity 2. Empyema cavity 3. Sputum; 4. Gastric	S S S
(8)	E.D. (LAS-131)	8/26/49	146	0	1. Pneumonectomy: Cavity 2. Sputum; 3. Gastric	R R
(9)	J.W.	9/ 6 /49 9/13/49	250	0	1. Cavernostomy drainage 2. Sputum 3. Gastric 4. Cavernostomy (2nd specimen)	CR CR CR CR
(10)	J.P.	9/15/49	308	0	1. Cavernostomy drainage 2. Sputum 3. Gastric	CR CR CR

TABLE III (Continued)

CASE NO.	PATIENT	DATE	STREPTOMYCIN	PAS	MATERIAL	RESULTS
					1. Pneumonectomy: caseous area	VS
					2. Sputum	VS
(11)	R.B. (LAS-161)	10/25/49	68	1160	3. Gastric	VS
					Pneumonectomy:	
					1. Empyema cavity	VS
					2. Cavity, RUL	VS
					3. Cavity, RLL	VS
					4. Caseous nodule, RLL	VS
					5. Cellular tubercles, RUL	—
					6. Sputum	VS
(12)	B.M. (LAS-166)	11/ 2 /49	119	705	7. Gastric	VS
					Pneumonectomy:	
					1. Cellular nodule, LUL	CR
					2. Cavity, LUL	CR
					3. Cavity, LLL	CR
(13)	H.R. (LAS-167)	11/15/49	197	687	4. Sputum; 5. Gastric	CR
					Lobectomy, RUL:	
					1. Caseous nodule	R
					2. Basal cavity	R
(14)	E.C. (LAS-169)	12/ 2 /49	93	780	3. Sputum; 4. Gastric	R
					Lobectomy, RUL:	
					1. Apical cavity	VS
					2. Peripheral cavity	VS
					3. Caseous area	—
					4. Sputum	—
(15)	B.C. (LAS-173)	12/13/49	82	492	5. Gastric	VS
					Pneumonectomy:	
					1. Giant cavity, LUL	S
					2. Caseous area, LUL	VS
					3. Cellular nodule, LLL	—
					4. Fibrocaseous area, LUL	S
					5. Cellular nodule, bronchus	—
(16)	R.C. (LAS-176)	12/20/49	123	804	6. Sputum; 7. Gastric	S

TABLE III (Continued)

CASE NO.	PATIENT	DATE	STREPTOMYCIN	PAS	MATERIAL	RESULTS
					Lobectomy, RUL:	
					1. Cellular nodule, bronchus	VS
					2. Fibrocaseous area	VS
					3. Sputum	VS
(17)	P.H. (LAS-177)	1/ 4 /50	90	360	4. Gastric	VS
					Pneumonectomy:	
					1. Caseous area, LUL	VS
					2. Cavity, LLL	VS
(18)	R.V. (LAS-180)	1/13/50	42	108	3. Sputum; 4. Gastric	VS
					Pneumonectomy:	
					1. Caseous area	S
(19)	R.S. (LAS-183)	1/17/50	96	2624	2. Sputum; 3. Gastric	S
					Lobectomy, LLL:	
					1. Fibrocaseous area	R
(20)	J.M. (LAS-184)	1/20/50	100	852	2. Sputum; 3. Gastric	R
					Pneumonectomy:	
					1. Caseous area, LUL	—
					2. Cellular nodule, LUL	—
					3. Caseous area, LLL	—
					4. Cellular nodule, LLL	—
					5. Empyema sac	S
(21)	W.L. (LAS-185)	1/24/50	74	240	6. Sputum; 7. Gastric	S
					Pneumonectomy:	
					1. Caseous area	S
					2. Fibro-calcific area	S
(22)	F.C. (LAS-187)	2/14/50	48	576	3. Sputum; 4. Gastric	S
					Pneumonectomy:	
					1. Caseous area	—
(23)	E.M. (LAS-207)	4/ 4 /50	80	0	2. Sputum; 3. Gastric	—
					Cavity enucleation, RUL:	
					1. Cavity	R
(24)	F.D. (LAS-210)	4/ 6 /50	54	1620	2. Sputum; 3. Gastric	R

TABLE III (Continued)

CASE NO.	PATIENT	DATE	STREPTOMYCIN	PAS	MATERIAL	RESULTS
					Pneumonectomy:	
					1. Cavity, LUL	S
					2. Cavity, LLL	S
					3. Empyema	S
(25)	C.M. (LAS-219)	5/ 9 /50	90	0	4. Sputum; 5. Gastric	S
					Lobectomy, RUL:	
					1. Cavity	R
(26)	F.F. (LAS-220)	5/16/50	47	1532	2. Sputum; 3. Gastric	R
					Pneumonectomy:	
					1. Cavity	S
					2. Fibrocaseous area	S
(27)	V.P. (LAS-229)	6/13/50	90	2060	3. Sputum; 4. Gastric	S
					Lobectomy, RUL:	
					1. Cavity	VS
					2. Cellular tubercles	VS
(28)	E.K. (LAS-242)	7/25/50	21	0	3. Sputum; 4. Gastric	VS
					Lobectomy, RUL:	
					1. Cavity	S
(29)	A.B. (LAS-248)	8/ 8 /50	48	0	2. Sputum; 3. Gastric	S
					1. Cavernostomy drainage:	CR
(30)	G.S. (LAS-249)	8/ 9 /50	206	2460	2. Sputum; 3. Gastric	CR
					Lobectomy, RUL:	
					1. Cavity	R
(31)	A.R. (LAS-266)	10/13/50	122	410	2. Sputum; 3. Gastric	R
					Lobectomy, LUL:	
					1. Cavity	VS
(32)	B.R. (LAS-302)	12/19/50	45	400	2. Sputum; 3. Gastric	VS
					Lobectomy, LUL:	
					1. Cavity	VS
					2. Fibrocaseous node	VS
(33)	E.F. (LAS-319)	1/30/51	39	2120	3. Sputum; 4. Gastric	VS

the work reported here; they reported results very similar to ours obtained in surgical material. No reports of similar studies on animal material has been found.

Discussion

The variability, plasticity and adaptability to the environment of bacteria are far greater than might be inferred from the rather narrow range of characteristics selected to identify them under the practical conditions of the Clinical laboratory (Topley and Wilson,[16] Dubos[17]).

The large literature on the many types of bacterial variations deals chiefly with the environmental factors which impress changes on bacteria under cultural conditions *in vitro*. Very little use has been made of *in vivo* techniques. *Variations in virulence* are, from the standpoint of clinical and laboratory medicine, of great importance. Although changes in virulence may be induced by *in vitro* methods, the change in virulence of bacteria after growing in animal tissues is one of their most impressive characteristics. Injection of millions of organisms from a culture may be required to kill a mouse, but only five or six organisms taken from the dead mouse may be required to kill a second mouse. An ordinary Staphylococcus albus may by proper animal passage be made to acquire pigment production, hemolysin, and may as easily lose these properties on culture media. It is self-evident that the tissues of the animal body (particularly the inflammatory reaction) which are in closest contact with the bacteria, either furnish a favorable environment or exert an effect upon the bacteria in producing such changes.

The present study was motivated by this concept. It was a surprise, therefore, to find that in our material the different inflammatory reactions in these resected tuberculous lungs apparently had no influence on streptomycin resistance of the tubercle bacilli. It can only be concluded, however, that this one property of tubercle bacilli, namely streptomycin resistance, is apparently not influenced by variations in the inflammatory reactions of the tissues. It would not be justified to conclude from this that, in general, inflammatory reactions have no effect in producing bacterial variations. Dubos[17] makes a plea for new techniques in attacking the problem of bacterial variations. *In vivo* techniques are worthy of wider exploration, and further work on this problem is in progress.

SUMMARY

This study was motivated by the expectation that the different kinds of inflammatory reactions in tuberculous lungs might be associated with differences in the degree of streptomycin sensitivity of the tubercle bacilli contained within them. Evaluation of this property in tubercle bacilli from 124 specimens obtained from 33 patients who had pneumonectomy, lobectomy or other surgical procedure demonstrated that this is not the case. Although many characteristics of bacteria are profoundly changed by the action of tissues, the development of streptomycin resistance by tubercle bacilli is apparently independent of such action.

RESUMEN

El motivo de este estudio es la posibilidad de que diferentes reacciones inflamatorias en los pulmones tuberculosos podrían estar asociados en grados diferentes de sensibilidad del bacilo de la tuberculosis contenidos en ellas, frente a la estreptomicina.

Se hace una estimación de esta propiedad del bacilo tomado de 124 especímenes de 33 enfermos a quienes se hizo neumonectomía, lobectomía u otros procedimientos quirurgicos, habiendose demostrado que en ellos no era así.

Aunque muchas características de los bacilos cambian profundamente por la acción de los tejidos, el desarrollo de estreptomicino-resistencia es aparentemente independiente de esta acción.

RESUME

Les auteurs sont partis de l'idée que la différence de sensibilité à la streptomycine des bacilles tuberculeux qui y sont contenus, pouvait conditionner les différentes réactions inflammatoires du poumon tuberculeux.

L'évaluation de la sensibilité de 124 spécimens de dabilles provenant de 33 malades ayant subi pneumonectomies, lobectomies ou autres résections pulmonaries, montre qu'il n'en est rien. Quoique bien des caractères du bacille soient profondément modifiés par l'action des tissus, il ne semble pas que l'apparition de la streptomycine-résistance y ait un rôle quelconque.

REFERENCES

1 Pyle, M. M.: "Relative Numbers of Resistant Tubercle Bacilli in Sputa of Patients Before and During Treatment with Streptomycin," *Pros. Staff Meet.*, Mayo Clinic, 22:465, 1947.

2 Steenken, Wm., Jr.: in Riggins, H. M. and Hinshaw, H. C. "Streptomycin and Dihydrostreptomycin in Tuberculosis," *Trans. Nat. Tuberc. Asso.*, pp. 39 to 57, 1949.

3 Yegian, D. and Vanderlinde, R. J.: "The Resistance of Tubercle Bacilli to Chemotherapeutic Agents (A Review of Basic Biological Considerations)," *Am. Rev. Tuberc.*, 61:483, 1950.

4 Minutes of the Sixth Streptomycin Conference of the Veterans Administration. October 1948, pp. 167-174.

5 Karlson, A. G. and Needham, G. M.: "Determination of Streptomycin Sensitivity of Tubercle Bacilli by Use of Egg Yolk Agar Medium," *Proc. Staff Meet.*, Mayo Clinic, 23:401, 1948.

6 Wolinsky, E., Reginster, A. and Steenken, Wm., Jr.: "Drug Resistant Tubercle Bacilli in Patients Under Treatment with Streptomycin," *Am. Rev. Tuberc.*, 58: 335, 1948.

7 Bailey, Wm. H.: "Resistance of Mycobacterium Tuberculosis to Chemotherapeutic Agents," *Am. Jour. Clin. Pathology*, 21:241, 1951.

8 Saenz, A. and Canetti, G.: "La streptomycino-resistance du bacille de Koch en fonction de la dose de streptomycine administree," *Rev. de la tuberc.*, 13, No. 9-10, 1949.

9 Delaude, A., Karlson, A. G., Carr, D. T., Feldman, W. H. and Pfuetze, K. H.: "Increase in Resistance of Tubercle Bacilli to Sodium-P-Aminosalicylic Acid: Observations on Cultures Isolated from Patients During Chemotherapy," *Proc. Staff Meet.*, Mayo Clinic, 24:241, 1949.

10 Karlson, A. G., Delaude, A., Carr, D. T., Pfuetze, K. H. and Feldman, W. H.: "The Occurrence of Tubercle Bacilli Resistant to P-Aminosalicylic Acid (PAS)," *Dis. of Chest*, 16:667, 1949.

11 Lehman, J.: "The Treatment of Tuberculosis in Sweden with Para-Aminosalicylic Acid (PAS). A Review," *Dis. of Chest*, 16:684, 1949.

12 Bloch, R. G., Vennesland, K., Ebert, R. H. and Gomori, G.: "The Effect of Streptomycin, Para-Aminosalicylic Acid (PAS) and Their Combination on the Tubercle Bacillus in vitro and in vivo," *Am. Rev. Tuberc.*, 59:554, 1949.

13 Vennesland, K., Ebert, R. H. and Bloch, R. G.: "In Vitro Effect of Streptomycin and Para-Aminosalicylic Acid on the Growth of Tubercle Bacilli," *Proc. Soc. Exp. Biol. Med.*, 68:250, 1948.

14 Dunner, E., Brown, W. B. and Wallace, J.: "The Effect of Streptomycin with Para-Aminosalicylic Acid on the Emergency of Resistant Strains of Tubercle Bacilli," *Dis. of Chest*, 16:661, 1949.

15 Medlar, E. M., Bernstein, S. and Reeves, F. C.: "The Demonstration of Streptomycin-Resistant Tubercle Bacilli in Necropsy Specimens," *Am. Rev. Tuberc.*, 63:449, 1951.

16 Wilson, G. S. and Miles, A. A.: "Topley and Wilson's Principles of Bacteriology and Immunity," The Williams and Wilkins Co., Baltimore, 1946, pp. 288-309.

17 Dubos, R. J.: "The Bacterial Cell," Harvard Univ. Press, Cambridge, 1947, pp. 135-228.

Clinical Observations on the Use of Isoniazid in Tuberculosis*

HOWARD M. PAYNE, M.D., ROBERT L. HACKNEY, JR., M.D., EUGENE A. CLARK, M.D. and PRESTON C. JOHNSON, M.D.
Washington, D. C.

Many investigators have advised that isoniazid dosage can safely exceed the 3 to 4 mg. per kilo level originally used in this hospital. Increased therapeutic effectiveness might result from increased dosage. In order to test for toxic effects it was determined to increase uniformly the isoniazid dosage of all patients not on a fixed study program to 400 mgs. a day. This plan resulted in double observations on 31 patients whose dosage per kilo was increased to 7 to 13 mgs. per kilo from 3 to 6 mgs. per kilo (Table I).

TABLE I

DISTRIBUTION OF PATIENTS BY REGIMENS

Regimen	Number of Patients	Number Observed at 400 mg./day	Number of Observations
INAH + SM	15	2	17
INAH + PAS	14	13	27
INAH + Sulfone	16	3	19
INAH Alone	24	13	37
TOTAL	69	31	100

Seven other patients were given 400 mgs. per day from the start of treatment (Table II).

Two patients of the 31 observed for two dosages were losing weight on 6 mg. and 4 mg. per kilo. On increasing the dose to 8 mg. and 6 mg. per kilo respectively, these patients gained weight (+0.7 and +4.0 percentage points of normal per month). One showed no weight change on either 4 mg. per kilo or 8 mg. per kilo. Of 15 who had been gaining on dosages of 3 to 6 mg. per kilo, eight lost from 0.7 per cent to 6.0 percentage parts of normal weight per month on the increased dosage schedule. Seven did not continue the tendency to gain (Table III).

Of the 15 on the changed regimen who failed to gain or who lost weight none showed positive sputum, x-ray or clinical worsening. The 13 remaining patients observed for two schedules continued to gain weight on the larger dosage as they had on the smaller.

*From the Division of Chronic Chest Disease; College of Medicine, Howard University.

The metabolic and nursing observations reported are made possible by a grant from the Shrine Tuberculosis and Cancer Research Foundation, Inc.

TABLE II

WEIGHT CHANGE IN PERCENTAGE PARTS OF USUAL NORMAL WEIGHT PER MONTH OF OBSERVATION BY RANGE OF ISONIAZID DOSE PER KILO

Weight Change Per Month of Observation	NUMBER OF PATIENTS	
	3 to 6 mg. Dosage	7 to 13 mg. Dosage
Gain in Percentage Parts:		
+5.00 or more	4	6
+3.00 - 4.99	11	2
+2.00 - 2.99	10	2
+0.1 - 1.99	25	8
No change	3	10
Loss in Percentage Parts:		
−0.1 - 1.99	11	7
−2.00 - 2.99	2	1
−3.00 - 4.99	1	1
−5.00 or more	0	1
TOTAL	64	38

Of the 64 patients in the 3 to 6 mg. dosage range, eight lost weight (12 per cent): 11 either lost or failed to gain (17 per cent).

Of the 38 patients in the 7 to 13 mg. dosage range, 10 lost weight (26 per cent): 20 either lost or failed to gain (52 per cent).

TABLE III

WEIGHT CHANGE IN PERCENTAGE POINTS OF NORMAL PER MONTH FOR EIGHT PATIENTS WHO LOST WEIGHT ON AN INCREASE OF DOSAGE

Gain:	6 mgs.		4 mgs.	4 mgs.				
+5.00 or more	xxx		xxx	xxx				
	xxx		xxx	xxx				
+3.00 - 4.99	xxx		xxx	xxx				
	xxx		xxx	xxx	4 mgs.			
+2.00 - 2.99	xxx		xxx	xxx	xxx			
	xxx	5 mgs.	xxx	xxx	xxx	4 mgs.	5 mgs.	4 mgs.
+0.1 - 1.99	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
Loss:	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
−0.1 - 1.99	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xxx
	xxx	xxx	xxx	6 mgs.	xxx	6 mgs.	9 mgs.	7 mgs.
−2.00 - 2.99	xxx	xxx	xxx		xxx			
	8 mgs.	xxx	6 mgs.		xxx			
−3.00 - 4.99		xxx			xxx			
		xxx			xxx			
−5.00 or more		xxx			xxx			
		9 mgs.			8 mgs.			

Relationship of Weight Gain to Normal Weight

Because it has been said that persons at or near 100 per cent of normal weight may expect little change due to isoniazid, this was investigated. Normal weight is based upon the statement of the patient of his best usual weight (Table IV).

TABLE IV: FAILURE TO GAIN WEIGHT OR LOSS BY PER CENT OF NORMAL WEIGHT AT THE START OF TREATMENT

At or above 7 mgs. per kilo: 33 patients

12 patients started at 100 per cent or more of normal; five lost or failed to gain.
9 patients started at 89.9 to 99.9 per cent of normal; five lost or failed to gain.
12 patients started below 89.9 per cent; two lost or failed to gain.

33

At or below 6 mgs. per kilo: 56 patients

16 patients started at 100 per cent or more of normal; three lost or failed to gain.
8 patients started at 89.9 to 99.9 per cent of normal; one lost or failed to gain.
32 patients started at less than 89.9 per cent; one lost or failed to gain.

56

Of the 41 starting drug regimens at all dosages at or above 90 per cent of their usual normal weight, 22 gained weight.

Other Toxic Symptoms

The observations of isoniazid toxicity reported in the literature range from irritability, nervous instability, constipation, anuria, to coma.

Subjective analysis of these phenomena is difficult. During the two month period of increased isoniazid dosage, there seemed to be an increasing number of complaints of rule violations among patients and of disregard for activity schedules.

Two nursing interviews and one medical were directed to questioning of each isoniazid patient on symptoms in the period of drug treatment. The medical, nursing and social service staff were also quizzed for objective comments concerning each patient. Only 97 observations were possible due to discharges.

Complaints of Unusual Symptoms or Behavior	
3 mgs./K to 6 mgs./K (69 patients)	7 mgs./K to 13 mgs./K (28 patients)
5 (7 per cent)	7 (25 per cent)

Table V lists complaints at the doses per kilo noted.

One patient at 4 mgs. per kilo, not tabulated, had exacerbation of a previously inactive duodenal ulcer. There have been no symptoms since stopping the drug. Pulmonary hemorrhage occurred in two others in the first month of treatment but was thought not to have any relationship to the drug regimen.

TABLE V

No. Patients	Complaints	Mg./Kilo			
3	Insomnia and general irritability	(8)	(4)	(6)	
4	Hyperactivity	(8)	(8)	(7)	(8)
3	Headache, constipation, anorexia	(9)	(4)	(9)	
2	Psychotic exacerbation	(4)	(4)		

Another untabulated out-patient who had a history of three abdominal operations for gastric ulcer received 6 mgs. of drug. He was normally apprehensive and high-strung. He had 5 mgs. per kilo of isoniazid for four months and improved dramatically. He died following development of volvulus which was not seen in time for successful operative care.

Evidences of Eighth Nerve Toxicity

Because there were a number of complaints of dizziness and vertigo, caloric stimulation tests were done on 82 patients distributed as follows. Unfortunately pre-treatment tests were not done (Table VI).

TABLE VI

CALORIC STIMULATION TESTS

	Number Tested	Number Abnormal
No previous Streptomycin or Viomycin:		
Streptomycin (1G bi-weekly) plus PAS (12G daily)	17	7 (41 per cent)
Viomycin Sulfate (2G bi-weekly) plus PAS (12G daily)	5	1 (20 per cent)
INAH alone or with oral PAS or Sulfone	36	7 (19 per cent)
INAH plus Streptomycin	1	1
Patients known to have previous Streptomycin or Viomycin:		
Streptomycin (1G bi-weekly) plus PAS (12G daily)	9	2 (22 per cent)
Viomycin (2G bi-weekly)	5	2 (40 per cent)
INAH alone or with PAS or Sulfone	9	8 (88 per cent)

Of those tested who had more than 6 mgs. per kilo of isoniazid for 1.5 months or more, there were 26 of whom 11 (42 per cent) had loss of response to caloric stimulation. Eleven of a total of 15 (73 per cent) toxic observations on 45 patients having isoniazid at the time of the test were related to higher dosage.

The number of tests here reported is small. However, there is a strong indication that isoniazid may accentuate evidence of damage to the vestibulam branch of the eighth nerve when streptomycin is being or has been given.

Audiograms were made of 57 patients. There were no pre-treatment tests for comparison. Of these, six treated with isoniazid showed loss of hearing of significant degree above 2048 cps. All had a history of previous therapy with streptomycin.

Isoniazid treated patients usually showed audiometric curves above minus 5 decibels despite the fact that expected values for their age were somewhat lower.

The Relationship of Isoniazid to Blood Sugar Values

An impression that the insulin requirement of diabetic patients was decreased when isoniazid was employed in therapy, led to the suspicion that the drug exerted a specific effect upon glucose metabolism.

Fifteen fasting, non-diabetic patients were given 100 mgs. of isoniazid intramuscularly after the blood was drawn for a base specimen. While the patients were still fasting, hourly specimens were drawn for three successive hours. Table VII shows essentially no change in fasting blood sugar values which could be attributed to isoniazid effect.

TABLE VII

FASTING BLOOD SUGAR IN GRAMS PER CENT FOR 15 PATIENTS FOLLOWING INTRAMUSCULAR INJECTION OF 100 Mgs. OF ISONIAZID

Patient	Control	1 Hour	2 Hours	3 Hours
E.J.	100	98	89	86
B.W.	86	85	76	81
L.G.	104	100	89	89
J.J.	92	90	83	88
F.S.	96	90	90	93
H.H.	93	84	88	95
M.A	96	93	94	96
E.N.	98	94	90	96
I.G.	102	85	101	103
M.H.	104	86	102	104
W.D.	75	86	75	87
J.L.	115	111	107	111
R.P.	87	95	92	94
M.T.	80	75	66	78
Q.B.	98	95	81	80

Glucose tolerance tests were then done for 10, non-diabetic patients. These were done without isoniazid and several days later the tests were repeated following an intramuscular injection of 200 mgs. of isoniazid. The results are tabulated in Table VIII.

TABLE VIII

GLUCOSE TOLERANCE TESTS

Blood Glucose Levels in Grams Per Cent Prior to and Every Hour for Three Hours With and Without Intramuscular Injection of 200 Mgs. Isoniazid. (Non-diabetic Patients, Fasting)

Patient	Control	1 Hour	2 Hours	3 Hours
(1) H.T.	83	120	101	—
(2) H.T.	83	129	112	90
(1) E.J.	97	129	95	—
(2) E.J.	97	124	97	92
(1) L.G.	91	124	118	93
(2) L.G.	100	128	107	103
(1) J.L.	113	176	134	95
(2) J.L.	122	205	148	120
(1) M.A.	104	158	131	109
(2) M.A.	93	148	112	102
(1) H.H.	93	122	112	155
(2) H.H.	90	112	102	92
(1) E.N.	94	188	135	87
(2) E.N.	96	165	107	80
(1) M.H.	107	168	110	95
(2) M.H.	107	230	160	148
(1) P.R.	119	100	118	68
(2) P.R.	102	125	115	97
(1) L.H.	90	112	100	105
(2) L.H.	91	150	105	85

Key: (1)—Represents glucose tolerance.
(2)—Represents glucose tolerance with Isoniazid.

No significant change in the glucose tolerance curve was observed.

Five diabetic patients under treatment for tuberculosis were then given glucose tolerance tests with and without a 200 mg. intramuscular dose of isoniazid. All antituberculous medication was withheld for 48 hours previously (Table IX).

No specific effects appear to be exerted on the glucose metabolism by isoniazid either for non-diabetics or diabetics.

Subsequently, a review of records of diabetic patients suggests that antimicrobial therapy has lead, in most instances, to control of the tuberculous disease to the extent that control of diabetes becomes possible with a lessened daily insulin dosage. With isoniazid, control of tuberculous progression is more rapid and the insulin requirement is more rapidly diminished than with streptomycin-PAS on standard intermittent regimens.

TABLE IX: BLOOD GLUCOSE LEVELS IN GRAMS PER CENT FOR FIVE DIABETIC PATIENTS FOLLOWING THE INGESTION OF 100 GRAMS OF GLUCOSE TESTED WITH AND WITHOUT INTRAMUSCULAR INJECTION OF 200 Mgs. OF ISONIAZID

Patient	Control	1 Hour	2 Hours	3 Hours
R.R. — Urine	1+	2+	4+	4+
(1)	235	368	ND	350
Urine	Neg.	Neg.	4+	4+
(2)	155	257	308	260
S.S. — Urine	Neg.	Neg.	Neg.	Neg.
(1)	145	185	194	148
Urine	Neg.	Neg.	Neg.	Neg.
(2)	116	155	182	154
E.J. — Urine	Neg.	4+	4+	4+
(1)	205	341	310	253
Urine	Neg.	Neg.	Neg.	Neg.
(2)	192	308	263	252
L.W. — Urine	Neg.	1+	Neg.	Neg.
(1)	108	252	182	132
Urine	Neg.	Neg.	Neg.	Neg.
(2)	125	271	202	148
M.C. — Urine	Neg.	Neg.	Neg.	Neg.
(1)	125	260	254	216
Urine	Neg.	Neg.	Neg.	Neg.
(2)	104	206	244	218

Key: (1)—Represents glucose tolerance.
(2)—Represents glucose tolerance following 200 mgs. of Isoniazid intramuscularly.

Parenteral Use of Isoniazid

Isoniazid intramuscular* 100 mgs. in 2 cc. of distilled water was given daily to 15 patients for 10 days. Burning at the injection site was reported to be equivalent to that observed with the injection of 1 gram of dihydrostreptomycin sulfate diluted to 2 cc. in distilled water. Toxic general symptoms were not observed at this dosage.

Subsequently a molecular combination of streptomycin sulfate, 1 gram and isoniazid, 236 mgs. was made available.** This preparation was diluted to 3 cc. with 2.1 cc. of distilled water. Ten patients were given daily injections of this product for 10 days. Local irritation was minimal and soreness subsided after a few hours. Careful interviews gave no evidence of systemic toxicity for these patients.

Blood and spinal fluid levels reported by Hobby et al† are charted for seven patients in Table X.

*Cotinazin Intramuscular, supplied by Chas. Pfizer & Co., Inc.

**Streptohydrazid, supplied by Dr. Gladys Hobby, Research Division, Chas. Pfizer & Co., Inc.

†Research Division, Chas. Pfizer & Co., Inc.

TABLE X

"Serums and spinal fluids were tested from a series of patients who had received streptohydrazid in dosages equivalent to 1 gm. streptomycin daily and 236 mg. of isoniazid daily. These specimens were tested in a microbiological assay using: (a) K. pneumoniae and (b) M. tuberculosis, H37Rv as the test organisms. It was assumed that, since streptohydrazid in its unhydrolyzed form is inactive against K. pneumoniae, serum levels detected with this organism would indicate the presence of free streptomycin base (e.g., they would indicate that the streptohydrazid had hydrolyzed in vivo). It was assumed further that M. tuberculosis would detect both streptomycin and isoniazid, and serum levels detected with this organism would be a satisfactory measure of the antituberculous activity of these specimens. Blood was drawn one-half hour after injection of streptohydrazid. Spinal fluid was taken at approximately two hours after the injection."

Patient	Spec. No.	Type Spec.	Organism for Test	Dilution Units	Mcg./ml.Δ	Organism for Test	Dilution Units▲	Mcg./ml.♦
W.A.	A1	Ser.	K. pn	8	6.64	H37Rv	12 (?)	25.80
	A2	Ser.	K. pn	64	53.12	H37Rv	96	206.40
	A3	Sp. fl.	K. pn	3	2.49	H37Rv	16	34.40
R.E.	E1	Ser.	K. pn	—	—	H37Rv	Neg.	Neg.
	E2	Ser.	K. pn	64	53.12	H37Rv	—	—
	E3	Sp. fl.	K. pn	Neg.	Neg.	H37Rv	8	17.20
R.M.	M1	Ser.	K. pn	—	—	H37Rv	Neg.	Neg.
	M2	Ser.	K. pn	32	26.56	H37Rv	48	103.20
	M3	Sp. fl.	K. pn	Neg.	Neg.	H37Rv	4	8.60
D.S.	SD1	Ser.	K. pn	4	3.32	H37Rv	Neg.	Neg.
	SD2	Ser.	K. pn	32	26.56	H37Rv	96	206.40
J.S.	SJ	Ser.	K. pn	—	—	H37Rv	3	6.45
	SJ2	Ser.	K. pn	48	39.84	H37Rv	64	137.60
	SJ3	Sp. fl.	K. pn	Neg.	Neg.	H37Rv	6	12.90
R.R.	R1	Ser.	K. pn	16	13.28	H37Rv	4 (?)	8.60
	R2	Ser.	K. pn	32	26.56	H37Rv	192	412.80
	R3	Sp. fl.	K. pn	2	1.66	H37Rv	16	34.40
M.T.	T1	Ser.	K. pn	6	4.98	H37Rv	3	6.45
	T2	Ser.	K. pn	64	53.12	H37Rv	64	137.60

Δ Based on pure SM base as standard; endpoint = 0.83 mcg. per ml.
▲ 12 day readings (solid media).
♦ Based on Streptohydrazid (HCl) as standard; endpoint = 2.5 mcgs. total wt. per ml. or 2.15 mcgs. exclusive of HCl content per ml.

Comment: Since the K. pneumoniae assays were conducted in broth, and the H37Rv assays in a solid medium with blood, the two sets of data are not strictly comparable. However, the fact that high serum levels were detected with K. pneumoniae indicates free streptomycin base was present. The high antituberculous activity appeared to be greater than the anti-klebsiella activity, which is consistent with the fact that both isoniazid and streptomycin exert an antituberculous effect, as does unhydrolyzed streptohydrazid also. Similar results were obtained with spinal fluids.

Subsequent testing indicates that hourly blood specimens show an increasing titre of streptomycin up to three hours and that although isoniazid levels decline slowly after the first hour, levels of 4 mcgs. or more are present for the third hour.

Discussion

Isoniazid is a drug which exhibits a wide range of toxic effects. These may be observed at a wide range of doses but more frequently at higher levels. The majority of toxic manifestations are of minor import. It is possible, however, that the behavioral symptoms may be missed if patients are not carefully observed. Minor degrees of general irritability, hyperactivity, and an increased tendency to over exertion are difficult to gage or distinguish from an increased sense of well-being due to clinical improvement. Frequent problems of discipline have been associated with isoniazid therapy at higher levels than 6 mgs. per kilo, whether a causative relationship exists is hard to determine.

A comparison of the rate of weight change for patients treated with 3 to 4 mgs. per kilo and then increased to a larger dosage (7 to 13 mgs. per kilo) raises the strong suspicion that weight loss may be a toxic effect of isoniazid in some patients rather than an evidence of clinical inefficacy.

Vertigo and hyperaesthesia occurred when isoniazid treated patients were given caloric stimulation tests. There is evidence also that isoniazid treatment accentuates the symptoms of neurotoxicity caused by streptomycin and viomycin when given concurrently or previous to isoniazid. There is no evidence that isoniazid increases the tendency of PAS to produce intestinal or gastric irritation although a slower rate of weight gain among these patients raises that presumption.

Dosages above 6 mgs. per kilo can be given. The incidence of toxic reactions increases slightly when this is done. Most of the toxic symptoms are mild. The response of patients to isoniazid is unpredictable on the basis of dosage alone. Only clinical observation and evaluation and determine the safety of any given dosage schedule.

In general isoniazid seems to accentuate neural tone in the autonomic nervous system and to increase the frequency of symptoms of neural irritation.

Patients who give a history of peptic ulcer, hypertonic or spastic colon or other illnesses linked to autonomic nervous system inbalance should be observed carefully when treated with isoniazid.

Caution should be employed when isoniazid dosages above 6 mgs. per kilo are given together with or following potentially neurotoxic drugs such as streptomycin or viomycin since their effects may be enhanced by isoniazid.

The occurrence of hyperactivity, personality changes, and a tendency to over exertion must be carefully weighed in relation to the general philosophy of tuberculosis treatment. Objective observation of these effects is difficult.

The relationship of isoniazid administration to blood sugar levels and glucose tolerance tests appears to be an indirect one. There is a suggestion that improved control of infection may be responsible for the reported cases

of lessened insulin requirement. Another possibility is that hyperactivity and increased muscular tone increase the catabolism of glucose and indirectly affect the insulin requirement in diabetes. This effect would not show when patients are closely watched for special tests.

Isoniazid parenterally in doses of 200 mgs. appears to be safe. Local irritation is slight both immediately and after 24 hours.

General toxic symptoms were not observed in the 10 patients reported treated for 10 days or in 20 treated with a molecular combination of streptomycin sulfate, 1 gram and isoniazid 236 mgs. for over three months on twice weekly schedules.

Possible advantages of this method of administration may lie in the certainty of the dosage for irresponsible, comatose, psychotic patients or others who refuse oral medication. The relatively high spinal fluid levels reported are worthy of comment.

Experience with schedules of streptomycin administration showed that bacterial resistance to a potent antimicrobial developed with less frequency on intermittent schedules. This was possibly due to less frequent exposure of bacillary colonies to sub-lethal blood or tissue concentrations of drug. It is known that tiny increments of streptomycin concentration in culture media will produce bacillary resistance in vitro. Daily oral isoniazid may, at least in chronic cavitary cases, produce too many periods during which the bacillary colonies are exposed to sub-lethal tissue levels of isoniazid. This consideration is speculative but the drug combination gives a new possibility for study.

CONCLUSIONS

1) Isoniazid toxicity is observed more frequently at dosages above 6 mgs. per kilo but may occur at any level.

2) Weight loss may be a symptom of isoniazid toxicity.

3) Isoniazid stimulates neural activity and may accentuate autonomic tone or exaggerate the symptoms of neurotoxicity from streptomycin.

4) Isoniazid has no direct effect upon blood sugar levels in normal or diabetic patients.

5) Isoniazid may be given safely in doses of 200 to 236 mgs. intramuscularly without serious toxic or irritative effect. This may be done either alone or in combination with streptomycin.

6) The intramuscular use of isoniazid-streptomycin combined is worthy of further study.

This study was made in association with the Cooperative Drug Research Program of the Field Research Branch, Division of Chronic Disease and Tuberculosis, Public Health Service, Department of Health, Education and Welfare.

CONCLUSIONES

1) La toxicidad de la isoniacida se observa más frecuentemente a las dosis arriba de 6 mg. por kilo, pero puede encontrarse a cualquier dosificación.

2) La pérdida de peso puede ser una manifestación de esa toxicidad.

3) La isoniacida estimula la actividad neural y puede acentuar el tono

autónomo o exagerar los síntomas de neurotoxicidad causados por la estreptomicina.

4) La isoniacida no tiene efecto directo sobre los niveles de la glucosa en la sangre de los sujetos normales o de lo diabéticos.

5) Puede darse con seguridad a lsa dosis de 200 a 236 mg. intramuscularmente sin efectos serios de carácter tóxico o irritativo. Esto puede hacerse sólo con ella o asociándola a la estreptomicina.

6) El uso intramuscular de la isoniacida merece más estudio.

RESUME

1) Les réactions toxiques de l'isoniazide s'observent le plus souvent lorsqu'on atteint des doses d'environ 6 mmgr. par kilogramme, mais elles peuvent apparaître à toutes les doses.

2) La perte du poids peut être une réaction toxique de l'isoniazide.

3) L'isoniazide aûgmente les réactions nerveuses, et peut exagérer les symptômes neuro-toxiques dûs à la streptomycine.

4) L'isoniazide n'a pas d'influence immédiate sur la glycémie aussi bien chez les diabétiques que chez les malades qui ne sont pas atteints de cette affection.

5) On peut administrer l'isoniazide sans inconvénient à des doses de 200 à 236 mmgr. par voie intra-musculare, sans qu'il y ait à craindre des conséquences importantes, soit toxiques soit irritatives. Un tel traitement peut être institué isolément ou combiné avec la streptomycine.

6) L'intérêt de l'utilisation d'une combinaison d'isoniazide-streptomycine administrée par voie intra-musculaire légitime un travail ultérieur.

Treatment of Pulmonary Tuberculosis with Isoniazide and Iproniazide*

SAMUEL COHEN, M.D., F.C.C.P. and ERIBERTO ANG, M.D.
Jersey City, New Jersey

I. *Introduction*

It has been definitely shown that the hydrazides of isonicotinic acid have anti-tuberculous activity in the test tube against the organism and in vivo in experimental animals.[1-6] A trial with isonicotinic acid hydrazide and its isopropyl derivative in the treatment of human tuberculosis was first reported by Robitzek, Selikoff and Ornstein in 1952.[7] Use of these drugs, especially isoniazide, has now become widespread. Their proper place in the treatment of tuberculosis, when used alone or in combination with other antibiotics or chemotherapeutic agents, and the comparative merit with "standard" antibiotic therapy (streptomycin and para-amino-salicylic acid), must still be determined.

The purpose of this report is to mention our experiences with the use of hydrazides of isonicotinic acid. Clinical studies with isoniazide (Rimifon†) were begun in this hospital January 6, 1952. Subsequently, the isopropyl derivative (Marsilid††) was also employed. A total of 76 patients were treated. The results are presented as of November 1, 1952.

II. *Selection of Patients*

The types of cases selected for study were as follows:

1) Patients with active advanced pulmonary tuberculosis who were on bed rest for a minimum of three months and who, in the past, had received chemotherapy—streptomycin (SM) or para-amino-salicylic acid (PAS) or both and who may or may not have had collapse therapy. Preference was given to patients who were febrile, had a stationary or declining weight curve, and associated mucous membrane tuberculous lesions. The roentgen status of these patients revealed either a stationary or progressive lesion.

2) Cases of acute bronchopneumonic exudative pulmonary tuberculosis, with or without associated obvious cavity, febrile, and in whom past experience indicated that reversibility of the lesion in whole or in part might be accomplished with streptomycin and PAS. Such patients received one of the hydrazides.

3) An intermediate group of patients with active pulmonary disease and positive sputum who had not shown significant improvement over a reasonable period of time (standard antibiotics may or may not have been administered).

4) An elective group of cases with bronchopleural or pleural-cutaneous fistulae—usually secondary to thoracic surgery.

---

*From Medical Division II of the Pollak Hospital for Chest Diseases, Medical Center, Jersey City, New Jersey.
These drugs († and ††) were available in 50 mg. scored tablets and supplied through the courtesy of Hoffman-LeRoche, Inc., Nutley, New Jersey.

III. *Method of Study*

Group I: This group consisted of two types of patients—total 59 cases: (a) those who received SM alone or in combination with PAS and were probably drug resistant—34 cases; (b) those who previously had not been treated with these drugs—25 cases. All of the patients received isoniazide according to the following approximate daily dosage schedule for a period of 90 days: 1.0 mg./Kilo body of weight for the first 30 days, 2.0 mg. for the second 30 days and 4.0 mg. for the last 30 days. A total of 39 patients from this parent group of 59 were available after 90 days of therapy and were then re-grouped in the following manner.

Group II: The patients who showed improvement on the x-ray film at the end of the above therapy period were continued on isoniazide in the

TABLE I: PRE-THERAPY STATUS OF PATIENTS

	Parent Group Treated with Isoniazide at first	Separate Group (5) Treated with Iproniazide at first
Total number of cases	59	17
Average Age (years)	45	49
Sex:		
Male	46	15
Female	13	2
Race:		
White	44	16
Colored	15	1
Known Duration of Tuberc.:		
1- 6 months	14	5
7-12 months	5	1
13-24 months	9	4
25-36 months	7	2
more than 36 months	24	5
NTA Classification:		
Moderately advanced	5	1
Far advanced	54	16
Previous Therapy:		
Pneumothorax	16	4
Pneumoperitoneum	7	3
Phrenicectomy	1	0
Thoracoplasty	7	1
Resection	4	1
Previous Chemotherapy: Courses of SM alone or		
in combination with PAS	34	11

TABLE II: EFFECT ON WEIGHT

	GROUP 1 ISO—90 days 59 Cases	GROUP 2 ISO—180 days 22 Cases	GROUP 3 ISO—90 days SM and ISO—90 days 6 Cases	GROUP 4 ISO—90 days IPRO—90 days 11 Cases	GROUP 5 IPRO—90 days 17 Cases
Patients lost weight prior to Rx	54 (91%)	22	6	11	14 (82%)
Patients gained weight during Rx	49 (83%)	21 (96%)	5 (83%)	9 (82%)	17 (100%)
Lost weight during Rx	6 (10%)	1 (4.5%)	1 (17%)	2 (18%)	0
Average weight gain (Pounds)	8	18	16.5	23.5	22.5
Maximum weight gain (Pounds)	28	38	31	37	38

dosage of 4.0 mg./Kilo body of weight for another 90 days—total 22 cases.

Group III: Those patients who revealed no roentgenological regression and had never received streptomycin were given streptomycin 1.0 gram every third day together with isoniazide daily (4.0 mg./Kilo body of weight) for a total of 90 days—total six cases.

Group IV: The patients who showed no x-ray film improvement and who previously had streptomycin were then placed on iproniazide on the dosage schedule of 1, 2, 4 mg./Kilo body of weight for a 90 day period similar to that used for Group I—total 11 cases.

Group V: These patients were separate and distinct from those included in the parent Group I and had not received isoniazide. Instead, they were given iproniazide in the approximate dosage of 1, 2, 4 mg./Kilo body weight for 90 days as outlined above—total 17 cases. Eleven of these cases had received streptomycin in the past.

Table I indicates some pertinent aspects of the pre-therapy status of patients in Group I (parent group) and Group V (independent group). (Other pre-therapy findings are referred to in subsequent tables for comparison with findings as result of therapy.)

During the entire study program, the patients were continued on the same dietary as previously. Cough sedatives were not used except in urgent situations, particularly with hemoptysis. No antipyretics were given to febrile patients.

There was close observation of the usual symptomatology of fever, weight curve, cough, expectoration and of possible toxic manifestations. During the period of therapy, laboratory examinations such as the x-ray film of the chest, hemoglobin, leucocyte count, sedimentation rate (Cutler Method) were done at 30 day intervals and urinalysis every 15 days. Sputum smears (concentrate) were repeated every 10 days and a specimen for culture was taken each month. Positive cultures were utilized for sensitivity studies. All of the above observations and determinations were, of course, also performed prior to therapy. In addition, the bromsulphalein test was done at the beginning and at the end of therapy. Laboratory tests which revealed abnormal findings related to toxicity were repeated post-therapy.

IV. *Results*

A) *Effect on Clinical Symptoms:*

1) *Fever:* Twenty-five cases (42 per cent) of the original group of 59 cases had fever (over 100 degrees F.) prior to the use of isoniazide. In 18 (72 per cent) there was return to normal temperature (100 degrees F. or below) at the end of 90 days of therapy. The drop in temperature was gradual in most cases and usually within the first two or three weeks. With the subsequent regimens, the temperature eventually returned to normal in these cases also. In the iproniazide treated group, disappearance of fever (nine cases or 53 per cent) was observed in all. It is of interest that reduction of fever was noted in 22 of the 25 cases with the dose of 1.0 mg./Kilo body of weight of isoniazide and in seven of the nine cases

TABLE III: CHEST X-RAY FINDINGS

	GROUP 1 ISO—90 days 59 Cases	GROUP 2 ISO—180 days 22 Cases	GROUP 3 ISO—90 days SM and ISO—90 days 6 Cases	GROUP 4 ISO—90 days IPRO—90 days 11 Cases	GROUP 5 IPRO—90 days 17 Cases
BEFORE THERAPY:					
Progressive	42 (71%)	18 (81%)	3 (50%)	6 (55%)	14 (82%)
Stationary	17	4	3	5	3
Exudative and/or caseous, with cavity	22	7	4	3	8
without cavity	2	1	1	0	2
Productive, with cavity	16	5	1	3	2
without cavity	4	0	0	1	0
Mixed, with cavity	15	5	0	4	4
without cavity	0	4	0	0	1
AFTER THERAPY:					
Regression	31 (52%)	15 (68%)	2 (33%)	2 (18%)	10 (59%)
Size of cavity	12	7	0	2	3
Cavity not seen	0	1	0	0	0
Infiltration	15	7	2	0	7
Cavity and infiltration	4	0	0	0	0
Progression	4 (7%)	2 (9%)	0	3 (27%)	2 (12%)
Size of cavity	1	0	0	2	0
Infiltration	3	3	0	1	2
No change	24 (41%)	5 (23%)	4 (67%)	6 (55%)	5 (30%)

with the same dose of iproniazide. Reduction of febrile toxicity was more dramatic in the iproniazide treated cases.

2) *Weight:* Table II summarizes the weight changes. It is seen that while 54 cases (91 per cent) of Group I lost weight prior to therapy, an average of 88 per cent gained weight thereafter on the various schedules. While 82 per cent of those treated with iproniazide alone lost weight before treatment, 100 per cent of the cases accrued weight with the drug. By comparing Groups I and V, it is noted that iproniazide appears superior to isoniazide, the average weight gain being 22.5 pounds for the former and eight pounds for the latter for the same length of time (90 days). There appears to be slight superiority in the group treated with iproniazide compared to the groups treated with 180 days of isoniazide or streptomycin plus isoniazide. A few cases in Group IV continued to add weight after remaining stationary for awhile with the earlier use of isoniazide.

3) *Subjective Improvement:* All of the patients were aware that they were receiving new drugs. Improvement in general well being and energy and vigor was observed in 85 per cent of patients getting isoniazide alone and in 93 per cent on iproniazide therapy. The remainder were either unimproved or felt worse.

4) *Cough and Expectoration:* Reduction in the quantity of sputum with a definite change in its character and associated diminution in cough occurred in 60 to 100 per cent of patients treated in the entire series (the former percentage in Groups IV and V and the highest in Group III). In about 50 per cent of cases, the sputum was reduced by at least one-half. In 2 per cent, the expectoration actually increased. In our experience, the isoniazide produced a more favorable response than did the iproniazide alone. The dosage of either drug (whether 1.0 or 4.0 mg.) made no real difference.

B) *Effect on Roentgenographic Changes:*

Table III briefly reflects the chest x-ray film findings just prior to and at the end of treatment. There appears to be no statistically significant difference in the regressive x-ray film changes noted with 90 days in Group I (52 per cent) as compared to Group V (59 per cent). Of the 39 cases subsequently followed in Groups II, III, IV, a total of 19 or almost 50 per cent showed further regression on x-ray film; 15 with 180 days of isoniazide and two each in Groups III and IV. Six months of isoniazide alone appeared superior in this regard to the regimens of these other groups. However, it is noted that in the streptomycin plus isoniazide treated group, not a single case revealed roentgen progression in contrast to the others.

About 45 per cent of the patients in Group IA (previously treated with streptomycin or streptomycin plus PAS) and about 60 per cent of patients in Group IB (previously not so treated) showed roentgenological improvement after a 90 day course of isoniazide.

In the parent group of 59, there were 53 cases (90 per cent) which had cavitation prior to therapy. Sixteen cases (30 per cent) showed diminution

TABLE IV: BACTERIOLOGY OF SPUTUM

	GROUP 1 ISO—90 days 59 Cases	GROUP 2 ISO—180 days 22 Cases	GROUP 3 ISO—90 days SM and ISO—90 days 6 Cases	GROUP 4 ISO—90 days IPRO—90 days 11 Cases	GROUP 5 IPRO—90 days 17 Cases
BEFORE Rx:					
Positive Smear	50	16	5	11	10
Positive Culture	53	17	5	11	15
AFTER Rx:					
Conversion of smear	2 (4%)	0	0	0	2 (12%)
Conversion by culture	15 (25%)	2 (9%)	1 (17%)	2 (18%)	4 (23%)
Conversion by smear and culture	21 (36%)	3 (14%)	1 (17%)	2 (18%)	2 (12%)
No change in smear and culture	19 (32%)	11 (50%)	3 (50%)	4 (36%)	7 (41%)
Reduced Gaffky count	2 (4%)	0	0	0	1 (6%)
Increased Gaffky count	0	1 (4.5%)	0	3 (28%)	1 (6%)
Turned positive	0	5 (22.5%)	1 (17%)	0	0

in cavitary size with 90 days of isoniazide. Of the total of 39 cases treated in Groups II, III, IV, nine cases or 28 per cent had decrease in size of cavity contrasted to 18 per cent in those treated in Group V with iproniazide alone. In only one case was residual cavity not visualized on laminography. As with streptomycin plus PAS therapy, the most marked roentgen effect was seen in the reversible exudative bronchopneumonic lesions.

The relationship between the dosage of hydrazide of isonicotinic acid and x-ray film changes revealed the following: 29 of the 59 cases in Group I or 50 per cent showed regressive x-ray film findings with the 1.0 mg./Kilo body of weight dose in addition to two other cases unimproved with smaller amounts. In Group V treated with iproniazide alone seven cases or 41 per cent revealed improvement with the 1.0 mg. dose.

C) *Effect on Bacteriology of Sputum* (Table IV):

The highest percentage (36 per cent) of conversion of sputum by smear and culture was seen in Group I. This was three times as high as among the cases treated with iproniazide (Group V) for a comparable period of time. However, it is important to observe that at the end of 180 days of therapy with the regimens in Groups II, III, IV, the conversion rate dropped and was about the same in each of these groups, averaging 16 per cent. The cases receiving isoniazide for 180 days had the highest rate of *reversion* to positive sputum (22.5 per cent).

D) *Correlation Between Bacterial Sensitivity Studies and Roentgenographic Changes:*

Bacterial sensitivity tests were performed on 32 positive cultures obtained from 23 patients who received one of the hydrazides alone; three cultures or 9.3 per cent showed resistant organisms to 1.0 microgram per ml. The average duration of therapy was 89 days. Two of these patients showed progression on the chest x-ray film and one no change. The remaining 29 cultures harbored sensitive organisms after an average treatment of 68 days. Regression was noted in 16 (55 per cent), progression in one (4 per cent) and no change in 12 (41 per cent).

E) *Effect on the Sedimentation Rate* (Cutler Method):

There was no correlation between the constitutional and roentgenological improvement on the one hand and this particular test. The decrease in the sedimentation rate for all groups ranged from 0 to 10 per cent, being highest in the parent Group I.

F) *Effect on Associated Clinical Conditions:*

1) *Bronchopleural fistula:* There were two patients in the series, who developed the complication post-operatively. In one patient, the sputum converted although air and fluid level persisted after 90 days of isoniazide. The second case revealed marked reduction in the tube drainage with isoniazide and later with iproniazide as compared to previous therapy with streptomycin and PAS.

TABLE V: SYMPTOMS OF TOXICITY

	GROUP 1 ISO—90 days 59 Cases	GROUP 2 ISO—180 days 22 Cases	GROUPS 4 and 5 IPRO—90 days 28 Cases
Total cases with toxic symptoms	27 (46%)	9 (42.5%)	17 (61%)
Vertigo	15 (25%)	2 (9%)	15 (53%)
Headache	7 (12%)	1 (4.5%)	4 (14%)
Nausea and/or vomiting	8 (13.5%)	2 (9%)	4 (14%)
Diarrhea	3 (5%)	1 (4.5%)	1 (3.5%)
Rash	2 (3.5%)	1 (4.5%)	1 (3.5%)
Insomnia	1 (1.7%)	1 (4.5%)	2 (7%)
Delayed urination	0	2 (9%)	0
Muscle Twitching	0	0	5 (18%)
Psychosis	0	0	1 (3.5%)
Drug Stopped	0	0	3 (10.5%)

2) *Pleural cutaneous fistula:* There was one patient with this complication and he showed marked reduction in drainage after 90 days of isoniazide therapy. He then signed release from the hospital.

3) *Tuberculous laryngitis:* The single patient in this category showed marked objective improvement with isoniazide and then with iproniazide 90 days each. The regression was more marked than had occurred with earlier treatment with streptomycin plus PAS.

4) *Multiple cold abscesses:* Following the institution of isoniazide, there was after 180 days, marked reduction in size of the abscesses with spontaneous disappearance of a few smaller ones.

5) *Miliary tuberculosis superimposed on far advanced cavernous tuberculosis:* One patient developed this complication after having been on prolonged streptomycin plus PAS therapy and artificial pneumoperitoneum refills. While reduction of toxicity and weight gain was apparent with 90 days of isoniazide, no significant change in the roentgen aspects was noted.

6) *Tuberculous empyema:* This followed spontaneous pneumothorax in one patient. Intercostal tube drainage was performed and he was given isoniazide. There was marked subjective improvement and decreased drainage. Later he received streptomycin plus isoniazide and improvement continued until a thoracoplasty was performed with obliteration of the space.

7) *Rheumatoid arthritis:* This patient was known to have rheumatoid arthritis for many years and received cortisone therapy at intervals. She was admitted to the hospital with cavitary tuberculosis. Marked symptomatic arthritic relief occurred with 90 days of iproniazide.

G) *Toxicity:*

1) *Clinical manifestations* (Table V): Various symptoms suggestive of toxicity were encountered during the course of therapy with isoniazide and iproniazide. Among them were vertigo, nausea, vomiting, headache, delayed urination, involuntary muscle twitchings and psychosis, the last two findings being present only in the iproniazide cases.

With isoniazide therapy, there was no material difference between the groups treated for 90 days and those for 180 days, toxic symptoms being present in 46 per cent in the former and 42.5 per cent in the latter. The symptoms were mild, transient and in no instance progressive. In most instances, these symptoms occurred in the first 30 days following the onset of therapy, lasted from a few days to a week and then gradually disappeared without additional medication. Vertigo was the most common untoward effect of isoniazide. Blood pressure readings in these cases showed a decrease of approximately 30 mm. and 20 mm. of mercury in the systolic and diastolic pressures, respectively. In no instance was it necessary to discontinue or reduce the dosage of isoniazide in Groups I and II.

The side effects were much more pronounced with iproniazide with a tendency to be progressive and occurred in 61 per cent of the cases. In three cases (10.5 per cent) the drug had to be stopped because of vertigo which was present in 53 per cent. Two of these patients were receiving 2.0 mg./Kilo body of weight per day and the other 4.0 mg. In one case,

the dosage of the drug was not increased and the 2.0 mg. schedule was maintained for 90 days. One patient with far advanced progressive tuberculosis, developed a psychosis while taking iproniazide and this complication must be listed as a contributory cause of death. Muscle twitchings were present in five cases. These two latter ill effects were not seen with isoniazide. Examination of the patients with intermittent twitchings showed some degree of hyper-reflexia but otherwise neurologically negative. Delay in the onset of flow of the urinary system was seen in two cases treated with isoniazide but not with iproniazide. Urinalysis in these two cases were negative and this phenomenon was found not to be progressive or persistent. Other side effects like vertigo, nausea, headache, insomnia, rashes were essentially similar to those resulting from isoniazide in their onset, duration and reversibility except that they tended to be more intense.

There were six deaths among all of the cases treated. Four died of their basic disease without complicating manifestations of toxicity from the use of the drugs. One who developed superimposed psychosis has been referred to above. The sixth death occurred suddenly. This patient had received 40 days of isoniazide without any previous signs of toxicity. There were no post-mortem examinations.

2) *Laboratory Examinations Detecting Possible Toxicity:*

(a) *Urinalysis:* Under isoniazide therapy for 90 days, 12 per cent of cases showed abnormal urinary findings contrasted to 36.5 per cent at the end of 180 days. These findings consisted of the presence of albumin, red blood cells or casts. Albumin in some patients was as high as 3 plus but disappeared spontaneously in the majority of cases. In others, abnormal findings gradually set in and disappeared slowly in the same manner until they became negative even while the patients were still receiving the medication. In a few cases, the above mentioned findings persisted until the termination of therapy and became normal during the post-therapy period. Granular casts (three to five per high power field) were seen in about 50 per cent of the cases with positive albumin. No instance of gross hematuria was encountered; abnormal number of red blood cells ranged from 15 to 30 per h.p.f. and this abnormal finding behaved in the same manner as albumin.

With iproniazide therapy, abnormal urinary findings were present in five cases (18 per cent) and regressed as they did in the isoniazide cases.

In all cases, all of the abnormalities reverted to normal except in those cases where they were present prior to the onset of therapy. These cases were not included in the above data. Neither drug in the doses used, aggravated preexisting abnormal urinary findings.

(b) *Hemoglobin:* In the group treated with 90 days of isoniazide, 29 cases (49 per cent) had a drop in hemoglobin by at least 20 per cent during therapy; only one such case was noted with 180 days of the drug while nine cases (32 per cent) exhibited a similar result in the iproniazide treated groups. This finding was usually confirmed on some subsequent examinations. The abnormal findings persisted up to the termination of drug therapy and in those cases with post-therapy observation, the majority

of patients recovered their initial hemoglobin level spontaneously without the benefit of hematinics.

There was nothing unusual as far as the leucocyte count was concerned which might conceivably be related to toxicity of the drugs.

(c) *Cephalin Flocculation Test:* In patients who received isoniazide for 90 days, a test of 2 plus or more was found in 36 per cent, and this rose to 64 per cent after 180 days. In Groups IV and V, receiving iproniazide, the incidence was 18 per cent. None of these showed any clinical evidence of liver damage and there was no instance of jaundice. Repeat values tended frequently to fluctuate considerably and the exact significance of the findings elicited is not apparent. The test finally became normal either during or post-therapy.

(d) *Bromsulphalein Test:* In Groups I and II, there were abnormal values in 9 per cent and in 14 per cent of those treated with iproniazide. Again, these findings could not be correlated with any clinical abnormality and their significance is difficult to interpret.

VI. *Comment*

It has been demonstrated that isoniazide and iproniazide have an inhibitory effect on the tubercle bacillus. On the basis of in vitro studies, using the Lowenstein-Jensen medium, the bacteriostatic effect of isoniazide alone was 10 times higher than that of streptomycin.[8] In addition, Barclay, et al.,[9] by means of the isotope tracer technique found that isoniazide was easily diffusible into dense caseous pulmonary lesions in high concentrations and that measurable amounts of the drug were still present in the blood of patients three to seven days after a single injection.

Our study confirmed the observations of Robitzek, et al.[10] in several respects. The systemic manifestations of pulmonary tuberculosis were more favorably influenced by iproniazide. The difference between isoniazide and iproniazide was most apparent in the toxic, febrile patient. Isoniazide was considerably less toxic than its isopropyl derivative. No final statement can now be made as to optimum dosage. Significant improvement, both subjectively and on the x-ray film was noted in a number of cases even with the small dose of 1.0 mg. per kilo body of weight of the hydrazides—given daily in three divided doses. Isoniazide, in the daily dosage of 4.0 mg. per kilo was well tolerated and is currently being maintained by us as an acceptable schedule. A daily dose of iproniazide in excess of 2 to 4 mg. per kilo body of weight is not justifiable. Our present view is, that because of the significant incidence and severity of toxic manifestations associated with this drug, that its prolonged use in the therapy of the average case of pulmonary tuberculosis is not warranted.

Roentgen regression, particularly of the exudative component, was about the same with both drugs. Actual non-visualization of cavitation (on laminography) occurred in only one instance. The incidence of sputum conversion by smear and culture was apparently significantly higher with isoniazide after 90 days of therapy compared with the same dosage schedule

of iproniazide given for the same length of time. However, this favorable trend with isoniazide was sharply reduced on the completion of 180 days of treatment.

Isoniazide has some definite advantages over streptomycin and PAS, in that it can be given by mouth as contrasted to streptomycin and it does not produce the gastro-intestinal irritation to the extent encountered with the use of PAS. Our experience indicates that streptomycin plus isoniazide is better tolerated by the patient than the combination of streptomycin and PAS. We believe that isoniazide is superior (on an objective basis) to PAS alone and probably the equal to streptomycin alone in the therapy of pulmonary tuberculosis. Only time will determine whether the streptomycin, isoniazide combination is as good or better than streptomycin plus PAS, as far as objective improvement is concerned.

The problem of isoniazide sensitivity is one of the most important aspects of drug therapy. Unfortunately, the findings in this study were based on a small number of cases and no definite conclusions are warranted. However, early emergence of resistant strains clinically has been reported[11] by the Medical Research Council of Great Britain which published its results in 331 patients treated with isoniazide for a period of three months. At the end of one month, cultures from 104 cases were tested and 11 per cent had resistant strains to 1.0 microgram per ml. After two months, tests of cultures were made from 58 cases and bacillary resistance was present in 30 or 52 per cent; seven of the 30 were resistant only to 1.0 microgram per ml., 23 resistant to 5.0 microgram per ml., and in 11 of these tested with higher concentrations, the 11 cultures showed growth at 50.0 microgram per ml. Similar tests performed in 21 cases at the end of three months of treatment revealed that 15 or 71 per cent were resistant and 13 of them to 5.0 microgram or more per ml. Their analysis indicated that the patients who developed resistance did less well as a group during the short period of observation than did those who harbored sensitive organisms. Thus, while the immediate prospect of improvement may be decreased in these cases, nevertheless it should be emphasized that bacterial resistance is separate and distinct from the natural resistance of the host to his disease and that objective improvement can continue despite the appearance of the former phenomenon. There is also some evidence that cross resistance of M. tuberculosis H37RV to isoniazide and iproniazide is the rule.[12]

It is apparent, therefore, that the hydrazides of isonicotinic acid are effective therapeutic agents by themselves but for a limited time. After several years of accumulated experience with the use of antibiotics and chemotherapeutic agents in pulmonary tuberculosis, there emerges this dominant thought—namely, the concept of long continued chemotherapy (preferably eight months or longer) by the administration simultaneously of multiple antibiotics or drugs in adequate dosage. Consequently, further studies are of paramount importance to determine the value of the combinnation of isoniazide with other drugs as regards clinical effectiveness and the lessening of drug resistance.

VII. SUMMARY

This report embraces the clinical experiences with 76 pulmonary tuberculous patients treated with isoniazide and/or iproniazide. The cases were divided into five groups: Group I (parent group) comprised 59 patients, of whom 34 at one time had streptomycin alone or in combination with PAS and the remaining 25 never had been treated with these drugs. They received isoniazide for a 90 day period on the following dosage schedule: 1.0 mg./Kilo body of weight for the first 30 days, 2.0 mg./Kilo for the second 30 days and 4.0 mg./Kilo for the last 30 days. The drug was given daily by mouth in three divided boses. After 90 days, 39 cases were available and were regrouped as follows: (a) Group II (22 cases) who showed roentgenological improvement earlier were continued for another 90 days on isoniazide in the dosage of 4.0 mg./Kilo; (b) Group III (six cases) had never received streptomycin and had shown no regressive roentgen changes with isoniazide alone for 90 days. They were subsequently given streptomycin gram 1.0 every third day plus isoniazide daily (4.0 mg./Kilo) over a span of 90 days; (c) Group IV (11 cases) showed no improvement on the chest x-ray film with isoniazide alone but previously had received streptomycin. These cases were placed on iproniazide alone in the dosage of 1, 2, 4 mg./Kilo body of weight for a 90 day period similar to that employed for Group I. Group V, an independent category of 17 cases, did not have isoniazide at any time. Instead, these patients received iproniazide for 90 days, again in the same manner as the preceding group.

Iproniazide was found to be superior to isoniazide in producing a more prompt reduction in febrile toxicity and in accelerating gain in weight. There was no significant difference in the regressive x-ray film changes noted with 90 days of therapy in Group I (52 per cent) as compared to Group V (59 per cent). Of the 39 cases followed in Groups II, III, IV, a total of 19, approximately 50 per cent, showed further improvement roentgenologically. The course of 180 days of isoniazide alone appeared superior in this respect than did the other regimens. However, in the streptomycin plus isoniazide treated group, there was not a single case that showed progression of the lesion. The most favorable therapeutic effect was observed in the resolution (of varying degree) of the exudative component of the parenchymal process. While reduction in size of cavitation was seen in a number of instances, non-visualization of cavity on laminography was found in only one of the 76 cases treated by the various regimens. After 90 days of therapy, the incidence of sputum conversion was three times higher with isoniazide (36 per cent) than with iproniazide (12 per cent). After 180 days of treatment in Groups II, III, IV, the conversion rate dropped considerably and averaged about 16 per cent.

Beneficial subjective and objective effects were seen with as low as 1.0 mg./Kilo body of weight daily of either hydrazide preparation. The dose of isoniazide now being used by us is 4.0 mg./Kilo daily.

Clinical manifestations of toxicity in the isoniazide treated cases occurred in 46 per cent and in the iproniazide group in 61 per cent. The most

common symptom encountered was vertigo. The symptoms with isoniazide were mild and transient while those with iproniazide tended to be more severe and progressive. For this reason, the latter drug is not advocated at present in the therapy of the average case of pulmonary tuberculosis. Laboratory findings indicative of possible toxicity have been discussed.

The number of bacterial sensitivity examinations made in this study were inadequate to form any conclusions. Other reports indicate a relatively early appearance of resistant strains of tubercle bacilli when patients are treated with isoniazide alone—and the occurrence of cross resistance between this drug and iproniazide. Isoniazide is a useful drug in pulmonary tuberculosis but is limited apparently by this factor of bacterial resistance. Further studies are necessary to determine its efficacy in combination with streptomycin or other drugs and its comparative value with the standard combination of streptomycin and PAS.

RESUMEN

Esta comunicación corresponde a la experiencia clínica con 76 casos de tuberculosis pulmonar, tratados con isoniacida o con iproniacida. Se dividen en cinco grupos: El grupo I, comprendió 59 enfermos de los que 34 alguna vez usaron estreptomicina sola o en combinación con PAS y los restantes 25 nunca habían sido tratados con esas drogas. Recibieron isoniacida por 90 días de acuerdo con la dosificación que sigue: 1 miligramo por Kilo de peso, durante los primeros 30 días; 2 mg. por Kilo, por los segundos 30 días; y 4 mg. por Kilo de peso, por los últimos 30 días. La dosis fué repartida en tres porciones al día y se usó por vía oral. Después de 90 días, se pudieron reclasificar 39 casos como sigue: (a) grupo II (22 casos) que mostraron pronta mejoría radiológica y se continuaron con isoniacida por otros 90 días a razón de 4 mg. por Kilo; (b) grupo III (6 casos) que nunca habían recibido estreptomicina y no mostraron cambios regresivos a los rayos X con isoniacida después de 90 días. A estos, se les aplicó enseguida estreptomicina, 1 gmo. cada dos días, además de isoniacida 4 mg. por Kilo por otros 90 días; (c) grupo IV (11 casos) que no mejoraron según la radiografía, pero que habían recibido antes estreptomicina. Estos casos fueron tratados con iproniacida sola, usando 1, 2 y 4 mg. por Kilo por noventa días de manera similar a la dosificación de la isoniacida en el primer grupo. Grupo V, independiente, de 17 casos que no se sujetaron al uso de isoniacida en ningún tiempo. En lugar de ella, recibieron iproniacida por 90 días de la misma manera que el grupo precedente.

La iproniacida, se encontró superior para producir una reducción más rápida de la toxicidad febril y para acelerar el aumento de peso. No hubo diferencias de importancia en los cambios regresivos a los rayos X a los 90 días, en el grupo I (52 por ciento) comparado con el grupo V (59 por ciento). De los 39 casos seguidos en grupos II, III y IV, un total de 19, aproximadamente 50 por ciento, mostraron ulterior mejoría radiológica. El tratamiento con isoniacida sola por 180 días, pareció superior en este respecto a los otros regímenes. Sin embargo, en grupo de isoniacida más estreptomicina, no hubo un sólo caso que mostrase empeoramiento de la lesión. El efecto tera-

péutico más favorable observado fué la resolución (de grado variable) del componente exudativo de los procesos parenquimatosos. Si bien la reducción del tamaño de la cavidad se vió en la mayoría de los casos, la desaparición de la cavidad de acuerdo con los hallazgos de la tomografía, se comprobó sólo en uno de 76 casos tratados por los varios regímenes. Después de 90 días, la incidencia de la conversión del esputo fué tres veces mayor con la isoniacida (36 por ciento) que con iproniacida (12 por ciento). Después de 180 días de tratamiento en los grupos II, III y IV, la proporción de la conversión cayó considerablemente y llegó a un término medio de 16 por ciento.

Se observaron efectos subjetivos y objetivos con dosis tan bajas como 1 mg. por Kilo diario con cualquiera de las dos preparaciones de hidracida. La dosis de isoniacida usada ahora, es de 4 mg. por Kilo.

Se presentaron manifestaciones clínicas de toxicidad a la isoniacida en 46 por ciento y a la iproniacida en 61 por ciento. El síntoma más comúnmente encontrado, fué el vértigo. Los síntomas con isoniacida fueron moderados y pasajeros en tanto que los observados con iproniacida fueron más severos y progresivos. Por esta razón la droga últimamente mencionada, no es aconsejada al presente en el tratamiento del caso medio de tuberculosis pulmonar. Se discuten los hallazgos de laboratorio que indican posible toxicidad.

El número de exámenes de sensibilidad bacteriana, fué inadecuado para formar conclusión alguna. Otros informes indican la aparición relativamente temprana de formas de resistencia del bacilo de la tuberculosis, cuando los enfermos son tratados solamente con la isoniacida así como la ocurrencia de la resistencia cruzada de esta droga con iproniacida. La isoniacida, es una droga útil en la tuberculosis pulmonar pero está limitado su uso aparentemente por este factor de la resistencia bacteriana. Se necesitan estudios ulteriores, para determinar su eficacia en combinación con la estreptomicina o con otras drogas así como su valor comparativo con la combinación estandar de estreptomicina-PAS.

RESUME

Les auteurs rapportent leur expériences cliniques portant sur 76 malades atteints de tuberculose pulmonaire, qui fut traitée par l'isoniazide ou l'iproniazide, ces produits pouvant être associés. Les cas furent divisés en cinq groupes. Le groupe I comprenait 59 malades dont 34 avaient été antérieurement traités par la streptomycine isolée, ou associée au P.A.S., les 25 autres malades n'avaient jamais été traités par ces produits. On les mit au traitement par l'isoniazide pendant une période de 90 jours, aux doses de 1 mmgr. par kilogramme de poids corporel pendant les premiers treinte jours, deux mmgr. pendant les trente jours suivants, et 4 mmgr. pour les trente derniers jours. Le produit fut administré chaque jour par voie buccale en trois fois. Après 90 jours, 39 malades furent regroupés: (a) le groupe II comportant 22 cas, comprenait les malades chez lesquels l'amélioration radiologique apparut le plus précocément. Dans ces cas, le traitement par l'isoniazide à la dose de 4 mmgr. par kilogramme fut continué pendant une nouvelle phase de 90 jours. (b) Le groupe III comprend

six malades qui n'avaient jamais été traités par la streptomycine, et pour qui l'isoniazide à titre isolé ne détermina aucune amélioration radiologique; en conséquence, on leur administra pendant 90 jours un gramme de streptomycine tous les trois jours, et quotidiennement de l'isoniazide à la dose de 4 mmgr. par kilogramme. (c) Le groupe IV comprend II observations de malades chez lesquels l'isoniazide isolé n'avait provoqué aucune amélioration radiographique mais ces malades avaient reçus précédemment un traitement par la streptomycine. Ils furent soumis alors à un traitement à l'iproniazide seul, à la dose de 1, 2 et 4 mmgr. par kilogramme pendant une période de 90 jours, de façon comparable à ce qui avait été fait pour le groupe I. Le groupe V comprend une catégorie particulière de 17 malades à qui l'on ne donna jamais d'isoniazide. Ils reçurent un traitement par l'iproniazide pendant une période de 90 jours de la façon indiquée précédenment.

L'iproniazide à semblé produire mieux que l'isoniazide une sédation rapide de la fièvre, et une accéleration de la progression du poids. Il n'y eut pas de modifications notables dans la régression des images radiologiques chez les malades traités pendant 90 jours, appartenant soit au groupe I (52%), soit au groupe V (59%). Parmi les 39 malades qui appartenaient aux groupes II, III et IV, 19 d'entre eux soit approximativement 50% eurent ultérieurement une amélioration radiologique. A ce point de vue, le traitement par l'isoniazide seul pendant 180 jours sembla supérieur aux autres modalités. Toutefois, dans le groupe où les malades furent traités par la streptomycine associée à l'isoniazide, il n'y eut pas un seul cas d'évolution. Les résultats thérapeutiques les plus heureux portèrent sur la résolution selon un degré variable, des processus pulmonaires exsudatifs. Tandis que dans certains cas, on nota une diminution des dimensions de la cavité, il n'y eut qu'un seul cas sur 76 traités par les différents procédés pour lequel la caverne disparut sur les tomographies. Après 90 jours de traitement, la disparition des bacilles de l'expectoration fut trois fois plus élevée dans les cas traités par l'isoniazide (36%) que dans les cas traités par l'iproniazide (12%). Après 180 jours de traitement, dans les groupes II, III et IV, la disparition des bacilles diminua considérablement et attint environ 16% en moyenne.

Des effets heureux, tant subjectifs qu'objectifs, furent constatés avec les deux préparations d'hydrazide, pour des doses aussi faibles que 1 mmgr. par kilogramme. Actuellement, le taux utilisé par les auteurs est de 4 mmgr. par kilogramme.

Des manifestations toxiques survinrent dans 46% des cas de malades traités par l'isoniazide, et dans 61% des cas chez les malades traités par l'iproniazide. Le plus courant des symptômes observés fut le vertige. Les symptômés toxiques dûs à l'isoniazide furent légers et transitoires, tandis que ceux qui furent constatés chez les malades traités par l'iproniazide eurent tendance à être beaucoup plus sévères et progressifs. C'est la raison pour laquelle les auteurs ne conseillent pas l'iproniazide pour le traitement des cas hatibuels de tuberculose pulmonaire. Les auteurs, discutent les

éléments de laboratoire qui peuvent indiquer l'existence d'une réaction toxique.

Les recherches de la sensibilité bactériologique qui furent pratiquées sont en nombre insuffisant pour permettre quelques conclusions. D'autres travaux ont montré une résistance relativement précoce chez les malades traités par l'isoniazide isolé, et l'existence de résistance croisée entre ce produit et l'iproniazide. L'isoniazide est un produit très utile dans le traitement de la tuberculose pulmonaire, mais il semble être limité par la possibilité de la résistance. Des travaux ultérieurs sont nécessaires pour déterminer son efficacité en association avec la streptomycine ou d'autres produits, et pour juger de sa valeur en comparaison avec le traitement classique par l'association streptomycine et P.A.S.

REFERENCES

1 Grunberg, E. and Schnitzer, R. J.: "Studies on the Activity of Hydrazine Derivatives of Isonicotinic Acid in the Experimental Tuberculosis of Mice," *Quart. Bull. Sea View Hosp.*, 13:3, 1952.

2 Zieper, I. and Lewis, R. A.: "Tuberculosis in a Macocus Rhesus Treated with Isonicotinylhydrazine," ¿? ¿? ¿?

3 Bernstein, J., Lott, W. A., Steinberg, B. A. and Yale, H. L.: "Chemotherapy of Experimental Tuberculosis: Isonicotinic Acid Hydrazide (Nydrazid) and Related Compounds," *Am. Rev. Tuberc.*, 65:357, 1952.

4 Steenken, W. S. Jr. and Wolinsky, E.: "Antituberculous Properties of Hydrazines of Isonicotinic Acid (Rimifon, Marsilid)," *Am. Rev. Tuberc.*, 65:365, 1952.

5 Benson, W. M., Stefko, P. L. and Roe, M. D.: "Pharmacologic and Toxicologic Observations on Hydrazine Derivatives of Isonicotinic Acid (Rimifon, Marsilid)," *Am. Rev. Tuberc.*, 65:376, 1952.

6 Rubin, B., Hassert, G. L. Jr., Thomas, B. G. H. and Burke, J. C.: "Pharmacology of Isonicotinic Acid Hydrazide (Nydrazid)," *Am. Rev. Tuberc.*, 65:392, 1952.

7 Robtizek, E. H., Selikoff, I. J. and Ornstein, G. G.: "Chemotherapy of Human Tuberculosis with Hydrazine Derivatives of Isonicotinic Acid," *Quart. Bull. Sea View Hosp.*, 13:27, 1952.

8 Colestos, R. J.: "De l'association I.N.H., Streptomycine, P.A.S.," *Rev. de la Tuberc.*, 16:670, 1952.

9 Barclay, W. R., Ebert, R. H., LeRoy, G. V., Manther, R. W. and Roth, L. J.: "Distribution and Excretion of Radioactive Isoniazide in Tuberculous Patients," *J.A.M.A.*, 151:1384, 1953.

10 Robitzek, E. H., Selikoff, I. J., Mamlok, E. and Tendlau, A.: "Isoniazide and Its Isopropyl Derivative in the Therapy of Tuberculosis in Humans: Comparative Therapeutic and Toxicologic Properties," *Dis. of Chest*, 23:1, 1953.

11 Medical Research Council: "The Treatment of Pulmonary Tuberculosis with Isoniazide," *Brit. Med. J.*, ¿?:735, 1952.

12 Schnitzer, R. J., Chief, Chemotherapy Laboratory, Research Department, Hoffman-LaRoche, Inc., Nutley, N. J.—Personal Communication.

Alternating Positive-Negative Pressures in Mechanical Respiration*

(The Cycling Valve Device Employing Air Pressures)

M. S. SEGAL, M.D., F.C.C.P.,** A. SALOMON, M.D., F.C.C.P.† and
J. A. HERSCHFUS, M.D.††
Boston, Massachusetts

The management of medical emergencies involving the retention of pulmonary secretions is an important therapeutic challenge.[1] Barach and his associates[2-6] suggested and developed several mechanical methods of eliminating accumulated secretions from the lungs in a variety of clinical entities. Recently[7] they reported the use of exsufflation with negative pressure (E.W.N.P.) by means of an apparatus by which the inspiratory and expiratory pressures were applied to the upper respiratory passageway with a mask or mouthpiece.▲ The effectiveness of this technique of eliminating retained bronchial secretions was ascribed to:[7,9] (1) Dilatation of the bronchial tree, as a result of the marked increase in lung volume associated with high inspiratory pressures, permitting air to pass into the alveoli beyond occluding mucous plugs or experimentally introduced mucin-thorotrast mixtures or metal foreign bodies, such as bullets or safety pins in dogs; and (2) The development of high expiratory flow rates occurring as a result of connecting the upper respiratory passageway at the peak inspiratory pressure with a high speed suction blower. The efficiency of the expiratory blast of air responsible for blowing secretions from the lungs was dependent upon the production of expiratory flow rates as large as or larger than those produced by maximal human coughing and two to three times higher than those found in patients with respiratory difficulties.[7] They briefly summarized the striking elimination of bronchial secretions or clearance of atelectasis in 39 of a composite group of 49 patients with poliomyelitis, Guillain-Barré syndrome, chronic bronchitis, bronchial asthma, pulmonary emphysema and bronchiectasis. They were able to achieve peak inspiratory pressures of 20 to 40 mm. Hg and peak negative pressures in 0.02 seconds. They reported expiratory flow rates 15 per cent higher than those produced by a cough of maximal effort in 15 normal individuals and approximately 100 per cent higher in 20 patients with bronchial asthma, pulmonary emphysema, bronchiectasis or polio-

*From the Department of Medicine, Tufts College Medical School and the Department of Inhalational Therapy, Boston City Hospital.
**Clinical Professor of Medicine, Tufts College Medical School and Director, Department of Inhalational Therapy, Boston City Hospital.
†Research Fellow in Medicine, Tufts College Medical School and Chief Resident, Department of Inhalational Therapy, Boston City Hospital.
††Assistant in Medicine, Tufts College Medical School.
▲The E.W.N.P. apparatus are manufactured by the Eliot Medical Plastics, Inc., Lynn, Massachusetts, and the O.E.M. Corporation, East Norwalk, Connecticut. The Eliot Exsufflator was used in this study.

myelitis. These studies were carried out with a variety of cycling valves employing one or two motor units for the positive and negative pressures.[7,8] These investigators found this form of mechanical respiration most helpful and even life saving in a variety of pulmonary and non-pulmonary diseases, wherein secretions have accumulated in the tracheobronchial tree.

Henderson[10] and Fenn[11] considered the respiratory effects of pressure breathing essentially similar, whether accomplished by the use of positive pressure applied to the upper respiratory passages or negative pressure applied to the body as in tank respirators. The circulatory effects of pressure breathing were clearly described by Barach and his associates.[12-14] They warned against the use of positive pressure in patients with circulatory insufficiency, stating that an excessive positive pressure within the chest also decreases the filling of the left side of the heart with a parallel fall in the systolic blood pressure.[12] Further evidence was given for the existence of a number of compensatory, homeostatic mechanisms which combine to maintain adequate circulation in the presence of the increased intrathoracic pressure associated with pressure breathing in normal subjects.[13,14] Among these mechanisms an increase in peripheral venous pressure and peripheral vasoconstriction, both help to restore the normal venous pressure gradient from the peripheral veins to the right auricle.[13,14] Whittenberger and Maloney and associates[15-17] have further advanced the above principles described by Henderson, Fenn and Barach et al. They stressed the value of expiratory negative pressure to promptly reconstitute the venous gradient and cardiac output as well as to prevent any further drop in blood pressure which may be observed in patients with peripheral circulatory collapse who have been injudiciously exposed to positive pressure breathing. Maloney et al[18] more recently stressed the importance of a negative pressure phase in mechanical respirators. They recommend the use of the alternating positive-negative pressure type of respirators, rather than intermittent positive pressure breathing—inspiratory (IPPB/I) alone when administering artificial respiration, to avoid the deleterious effects on the circulation that may be noted with the latter alone. They wisely pointed out that although intermittent positive pressure breathing has untoward effects in certain emergency situations, it undoubtedly will continue to be useful in increasing altitude tolerance, in certain forms of pulmonary therapy and during anesthesia in patients with normal circulation. We have found intermittent positive pressure breathing with the Bennett valve, employing bronchodilator aerosols during the inspiratory positive pressure phase most helpful in patients with chronic bronchial asthma and chronic pulmonary emphysema.[1,20]

Present Study

The purpose of this paper is to report our studies employing alternating positive-negative pressures (exsufflation with negative pressure) carried out with the Eliot Exsufflator Unit (Figure 1).

This valve was designed to supply gradual positive pressure breathing on inspiration followed by an instantaneous change-over to an extremely

rapid expiratory negative pressure, according to the principles advocated by Barach and his associates.[7,8] The portable Eliot Exsufflator Valve Unit was also employed in some of the observations of Barach and his associates.[8]

The unit consists principally of a cycling valve, the central core of which is actuated by two electrically operated magnetic solenoid switches. The solenoids are operated by a toggle switch placed in the front of the unit. The valve has three openings, two of which are connected to the inlet and exhaust apertures of a high speed motor blower unit which develops both positive and negative air pressures. The third opening is connected by means of clear plastic tubing to a face mask or mouthpiece. When the toggle switch is thrown to the inspiratory position, the central core of the valve slides horizontally to permit the inlet of positive pressure. When the toggle switch is thrown to the expiratory position, there is an instantaneous change-over to negative pressure.

The cycling valve, motor blower unit and connections are housed in a sturdy portable carrying case. The unit operates on AC current and is run quite simply by the patient, nurse, attendant or physician. The evacuated secretions are trapped in the plastic tubal connection and can easily be cleaned by separating the tube from the valve connection. The unit operates entirely on air pressure changes and hence does not require the use of oxygen tanks and regulators.

The patient is instructed to breathe quietly and slowly during inspiration and more forcibly during expiration. The length of inspiration should be encouraged to exceed that of expiration. The change-over from inspiration to expiration occurs almost instantaneously and is instituted at the peak

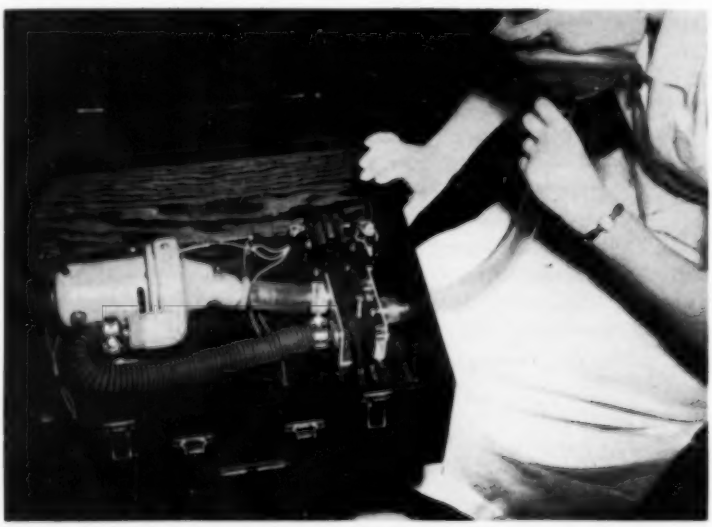


FIGURE 1: Eliot Exsufflator Unit.
Positive-Negative Pressure Phases.

of the inspiratory pressure. The patient should be encouraged to expire as rapidly and as completely as possible to obtain the beneficial effects of the rapidly developing peak of negative pressure.

Pressure Characteristics and Time Relationships of the Exsufflator.

The pressure characteristics and time relationships were studied in four normal subjects with vital capacities ranging from three to five liters. The plastic tubal connection from the exsufflator was connected directly to a face mask. A Sanborn electromanometer was connected to the face piece. The pressure changes were directly recorded on the Sanborn direct writer electrocardiograph. This highly sensitive recording unit made it possible to accurately record the time relationships and pressure changes which occurred during inspiration and expiration with the exsufflator. At the outset of the rapidly induced expiratory air flow, the subject was asked to simply breathe out rapidly to conform with the rapidly developed high expiratory negative pressure. This is referred to as a "single cough" (See Figure 2).

The exsufflator is capable of producing a maximum *range of* +30 mm. Hg inspiratory positive pressure and −30 mm. Hg expiratory negative pressure in relation to atmospheric pressure (baseline). A mean mask pressure for the entire cycle of +0.64 mm. Hg is achieved (See Figure 2). The inspiratory peak pressure, usually 30 mm. Hg, is reached in 2.48 seconds in this curve.

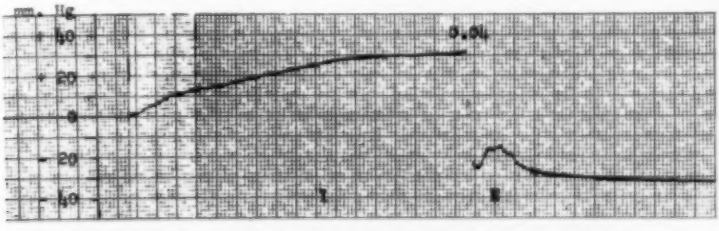


FIGURE 2: Face Mask—Eliot Exsufflator Valve, Pressure Curve
Positive-Negative Pressure—Single Rapid Exsufflation (0.04 Sec.)
Peak Inspiratory Pressure Occurs at 2.48 Seconds
Mean Pressure Entire Cycle = +0.64 mm. Hg.

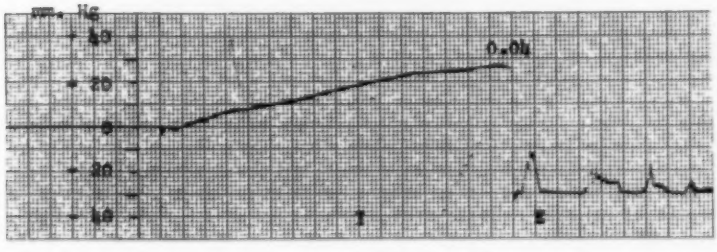


FIGURE 3: Face Mask—Eliot Exsufflator Valve, Pressure Curve
Positive-Negative Pressure—Series of Forced "Coughs"
Mean Pressure Entire Cycle = −0.14 mm. Hg.

The time interval for reaching the maximum inspiratory peak pressure can be varied by a simple adjustment of the screw set over the inlet valve. The peak of the expiratory negative pressure of 74 mm. Hg is achieved within the first 0.04 seconds of expiration,—*thus achieving a rapid expira-*

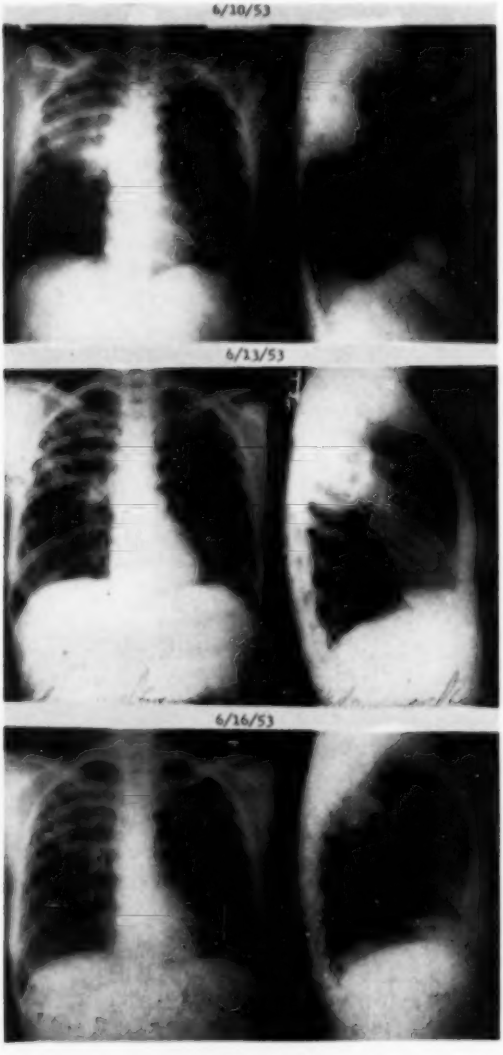


FIGURE 4

Top: Large homogenous area of consolidation in the posterior segment of the right upper lobe. Remaining lung fields clear. Pneumonic consolidation with abscess formation.—*Center:* Multiple irregular radiolucencies in the same segment, largest 4 cm. in diameter with fluid level suggesting excavating process.—*Bottom:* No fluid levels seen. Definite improvement noted.

tory flow rate of air. After the peak expiratory negative pressure has been reached, the face mask pressure then become less negative (16 mm. Hg) and gradually drops to 32 mm. Hg below the atmospheric (baseline), at the end of expiration, a total of 64 mm. Hg. Minor variations towards the slightly higher range of pressures may be obtained with some of the valves,—due to intrinsic variations in both current and motor power.

The pressure characteristics in the face mask were also studied in a normal subject during a series of coughs (Figure 3). The subject was also exhorted to cough at the switch-over to expiration from the height of inspiration, and another pressure curve tracing obtained. A peak expiratory pressure of 58 mm. Hg was achieved within 0.04 seconds during a single cough. A series of short coughs was continued to obtain additive effect in expelling secretions during the remainder of the expiratory negative cycle. The peak inspiratory pressure was 34 mm. Hg. The peak expiratory pressure was 58 mm. Hg. At the end of the series of coughs, the face mask pressure was 30 mm. Hg below atmospheric (baseline). The mean pressure during the entire cycle was −0.14 mm. Hg.

The rate of expiratory flow (movement of air from the lungs) exceeds that which can be produced by the patient himself (unaided) and may exceed that produced by a forceful cough from a normal subject.[13] It is the increased gradient of pressure established between the pressure in the inflated lungs at the beginning of expiration and the negative pressure in the face mask or mouthpiece which is responsible for the increased expiratory flow rate.

Clinical Application

The successful effects of the rapidly induced expiratory negative pressure are usually followed by the expectoration of sputum and retained secretions. These effects may be observed in some patients as long as one-half to one hour after a treatment, the secretions having been loosened previously but not evacuated.

Ten patients with chronic bronchiectasis in severely debilitated states have been able to keep themselves virtually free of all retained secretions for the past four months on continued hospital and home treatment. They have been instructed to employ six inhalations of Vaponefrin aerosol before each course of treatment which is given before meals and at bedtime. Treatment may also be given at any other time during intensive nonproductive coughing paroxysms. Usually eight to 10 applications with the exsufflator unit for each course is sufficient. During the course of treatment the patient is instructed to stop and expectorate whenever he has a mouthful of secretions. Frequently the sputum drains into the plastic tubing connecting the face piece to the valve. This can be easily washed out after treatment. Whenever indicated, patients are encouraged to follow a routine of thoracic and diaphragmatic breathing exercises after each treatment.

A dramatic and successful application of the exsufflator occurred in one of our acutely ill patients, which we are reporting in detail.

M.S. On June 4, 1953, a 34-year old white female with past history of excessive alcohol intake and respiratory infections was admitted for the second time to the Boston City Hospital, complaining of chest pain and dyspnea. During the first admission in 1946, she was treated for pneumonia of the left lower and right middle lobe. Sputum cultures revealed mixed flora. She responded promptly to treatment with penicillin. Six months prior to the present admission, she had a "severe cold" with cough and chills. She was treated at home with penicillin and responded promptly.

The present acute illness was characterized by fever, chilliness, chest pain and severe cough of several days' duration prior to admission. The admitting resident noted a temperature of 104 degrees F., slight icterus, marked dullness, pure bronchial breath sounds and moist rales over the right scapular and subscapular regions. Roentgenograms taken on admission, June 4, 1953, showed atelectasis with abscess formation of the posterior segment of the right upper lobe. The remaining lung fields were clear (Figure 4 *Top*). She was treated symptomatically and also started on penicillin. Her temperature dropped to normal the next day, but rose to 104 degrees F. the same evening. Roentgenograms on June 10, 1953, showed no change. On this day, the cough was productive of small amounts of brownish blood-tinged sputum. She appeared toxic and acutely ill.

Because of the possibility of obstructive type of atelectasis, it was decided to institute exsufflation therapy. Several inhalations of a bronchodilator aerosol were first administered. Then eight to 10 careful "coughs" were carried out with the Eliot Exsufflator, using the mouthpiece attachment. Large amounts of sputum were "coughed up," both during and after this treatment. This procedure was repeated the next day with similar results. The sputum filled the plastic tubing connecting the mouthpiece to the valve.

Repeat roentgenograms, taken three days later (June 13, 1953), showed clearly multiple irregular radiolucent areas in the same segment, the largest measuring 4 cm. in diameter with a fluid level suggesting an excavating process (Figure 4 *Center*). Therefore, she was treated again on two consecutive days with a series of exsufflations. Roentgenograms taken on June 16, 1953, showed complete disappearance of the fluid level and considerable improvement of the lung segment (Figure 4 *Bottom*).

The clinical course was most striking. She became afebrile and had no cough or expectoration after the first two days of treatment. After the fourth day of exsufflator therapy, she was placed on a daily regime of IPPB/I with antibiotics. No further improvement was noted on June 24, 1953, and this treatment was discontinued. Bronchoscopy and bronchography to establish the extent of lung involved and the advisability of subsequent resection are planned.

Essential laboratory data revealed the following: Six sputum cultures and as many sputum stains for acid fast bacilli were negative. A test with old tuberculin, 1-10,000 was negative but 1-1000 was positive. Gram stains revealed many gram positive diplococci. Pneumococci type III were found in two sputum cultures and in one blood culture. The hemoglobin was 10 Gm.; hematocrit, 33 per cent; erythrocyte sedimentation rate, 25 mm.; and the white blood count ranged from 12,100 to 9,500.

SUMMARY

1) The simple portable air pressure device is described which safely produces positive and negative phase pressures (exsufflation with negative pressure) without disturbing the circulatory hemodynamics during the brief periods of therapeutic application.

2) The pressure characteristics in the face mask obtained with this unit are recorded,—during a single cough and during a series of coughs.

3) The rapid expiratory air flows created are sufficiently capable of eliminating the accumulated pulmonary secretions in a variety of pulmonary and nonpulmonary diseases. We are presently applying this form of therapy in a series of patients with bronchiectasis, atelectasis of varied etiology and postoperative retention of pulmonary secretions.

4) A detailed case history is presented of the application of the device in a patient with a large atelectatic-cystic area of lung. Copious expectoration followed a series of "coughs" with the apparatus and a large cystic area was successfully evacuated.

5) Control settings added to the basic unit, to permit the use of wider pressure ranges during both positive-negative phases, are presently being explored for the purposes of resuscitation in general.

RESUMEN

1) Se describe un dispositivo sencillo de presión de aire que de manera segura produce presiones positiva y negativa (exuflación con presión negativa) sin perturbar la hemodinámica circulatoria durante los breves períodos de aplicación terapéutica.

2) Se registran las presiones características en el procedimiento de la mascarilla durante la tos simple y durante la serie de tos.

3) La rápida corriente de aire expiratorio creada, es suficiente para eliminar las secreciones acumuladas en una variedad de afecciones pulmonares y no pulmonares. Actualmente, estamos aplicando esta forma de tratamiento a una serie de enfermos con bronquiectasia, atelectasia de etiología diversa y retención postoperatoria de secreciones.

4) Se presenta un caso de aplicación del procedimiento en un enfermo con un área grande atelectásica y cística. Después provocadas en el aparato se obtuvo expectoración copiosa seguida de evacuación del área cística satisfactoriamente.

5) A la unidad básica se agregan mecanismos de control para permitir el uso de variantes de presión tanto durante la fase positiva, como durante la negativa y estos mecanismos se están ensayando para fines de empleo en resucitación.

RESUME

1) Les auteurs décrivent un appareil simple et portatif qui permet au cours de périodes limitées d'application thérapeutique, la production de pressions gazeuses positives et négatives (la pression négative correspondant à la phase d'exsufflation) sans entrainer de troubles de la circulation hémo-dynamique.

2) Ils ont recueilli les pressions caractéristiques obtenues dans le masque facial au cours d'un seul effort de toux ou au cours de secousses de toux en série.

3) Cet appareil crée une aspiration d'air lors de l'expiration qui est suffisante pour entrainer l'élimination des sécrétions pulmonaires dans une série d'affections atteignant ou non les poumons.

4) Les auteurs rapportent l'histoire détaillée d'une observation où l'ap-

pareillage à été appliqué chez un malade atteint d'une importante zone atélectasique et kystique du poumon. Une expectoration abondante suivit une série de secousses de toux provoquées par l'appareil, et permit l'évacuation des secrétions qui encombraient une importante région kystique.

5) Les auteurs sont actuellement en train d'étudier l'adaptation d'éléments de contrôle sur leur appareil de base, de façon à permettre la réanimation en général. Ils utilisent dans ce but une gamme plus étendue de pressions aussi bien au cours de la phase positive que de la phase négative.

REFERENCES

1 Segal, M. S. and Dulfano, M. J.: "Chronic Pulmonary Emphysema. Physiopathology and Treatment," New York City, Grune & Stratton, Inc., 1953.
2 Barach, A. L., Beck, G. J., Bickerman, H. A. and Seanor, H. E.: "Mechanical Coughing: Studies on Physical Methods of Producing High Velocity Flow Rates During the Expiratory Cycle," *Trans. Assn. of Am. Phys.*, 64:360, 1951.
3 Barach, A. L., Beck, G. J., Bickerman, H. A. and Seanor, H. E.: "Physical Methods Simulating Mechanisms of the Human Cough," *J. Applied Physiol.*, 5:85, 1952.
4 Bickerman, H. E., Beck, G. J., Gordon, C. and Barach, A. L., with Itkin, S.: "Physical Methods Simulating Mechanisms of the Human Cough: Elimination of Radiopaque Material from the Bronchi of Dogs," *J. Applied Physiol.*, 5:92, 1952.
5 Barach, A. L., Beck, G. J. with Smith, W. H.: "The Principles and Technic of Operation of the Exsufflator," *Am. Pract. and Dig. of Trtmnt.*, 3:733, 1952.
6 Barach, A. L., Beck, G. J., Bickerman, H. A. and Seanor, H. E.: "Physical Methods Simulating Cough Mechanisms," *J.A.M.A.*, 150:380, 1952.
7 Barach, A. L., Beck, G. J. and Smith, W. H.: "Mechanical Production of Expiratory Flow Rates Surpassing the Capacity of Human Coughing," *Am. J. Med. Sc.*, 226:241, 1953.
8 Beck, G. J., Barach, A. L. and Smith, W. H.: "Techniques of Exsufflation with Negative Pressure," *Modern Hospital*. To be published.
9 Cherniak, R. M., Gordon, C. A. with Drimmer, F.: "Physiological Effects of Mechanical Exsufflation on Experimental Obstructive Breathing in Human Subjects," *J. Clin. Investigation*, 31:1028, 1952.
10 Henderson, Y.: "Adventures in Respiration," Baltimore, Md., The Williams & Wilkins Co., p. 272, 1938.
11 Fenn, W. O.: OSRD, C.A.M., Rep. 111, p. 14, 1942.
12 Barach, A. L.: "The Therapeutic Use of Helium," *J.A.M.A.*, 107:1273, 1936.
13 Barach, A. L., Fenn, W. O., Ferris, E. B. and Schmidt, C. F.: "Physiology of Pressure Breathing: A Brief Review of Its Present Status," *J. Aviation Med.*, 18:73, 1947.
14 Beck, G. J., Seanor, H. E., Barach, A. L. and Gates, D.: "Effects of Pressure Breathing on Venous Pressure," *Am. J. Med Sci.*, 224:169, 1952.
15 Whittenberger, J. L. and Sarnoff, S. J.: "Physiologic Principles in the Treatment of Respiratory Failure," *M. Clin. No. America*, 34:1335, 1950.
16 Maloney, J. V. Jr., Otis, A. B., Fenn, W. O. and Whittenberger, J. L.: "Effect of Positive Pressure Breathing on Air Flow Resistance of the Tracheobronchial Tree," (Abstract), *J. Clin. Investigation*, 29:832, 1950.
17 Maloney, J. V. Jr.: "Therapeutics of Pressure Breathing," *Bull. New England M. Center*, 12:116, 1950.
18 Maloney, J. V. Jr. and Whittenberger, J. L.: "Clinical Implications of Pressures Used in the Body Respirator," *Am. J. Med. Sci.*, 221:425, 1951.
19 Maloney, J. V. Jr., Elam, J. O., Handford, S. W., Balla, C. A., Eastwood, E. W., Brown, E. S. and Ten Pas, R. H.: "Importance of Negative Pressure Phase in Mechanical Respirators," *J.A.M.A.*, 152:212, 1953.
20 Segal, M. S., Salomon, A., Dulfano, M. J. and Herschfus, J. A.: "Pressure Breathing—The Use of Intermittent Positive Pressure in the Inspiratory Phase of Respiration (IPPB/I)," *New England J. Med.*, 250:225, 1954.

Pulmonary Complications of Heart Diseases*

N. E. REICH, M.D., F.C.C.P.†
Brooklyn, New York

There was a time within the memory of living clinicians when the appearance of pulmonary signs during the course of many heart diseases was invariably described as "pneumonia" or "pleurisy". Our rapidly expanding knowledge has made it essential to consider carefully other possibilities if diagnosis and prognosis are to be accurate, and treatment is to be effective. Among these are certain congenital cardiac defects, acute and chronic inflammations of the heart and aorta, degenerative lesions of the coronary arteries and aorta, primary neoplasms of the heart, and chronic cor pulmonale. Although these lesions usually present certain distinguishing features, the criteria customarily employed in the diagnosis of each may occasionally be found wanting or unreliable. When the differential diagnosis proves difficult the detailed observation of the cardiac, pulmonary and pleural signs may offer considerable aid.

Congenital Lesions

The only congenital vascular lesions which directly affect the trachea or bronchi by direct compression are the vascular ring anomalies.[1] Other defects, such as tetralogy of Fallot, produce dyspnea, cyanosis, clubbing, etc., but these symptoms are due to lack of proper oxygenation of blood caused by the existence of abnormal shunts. It is significant that not all infants with cyanosis or dyspnea have congenital heart disease. A large diaphragmatic hernia, congenital air cyst, lung anomaly, or pulmonary hemorrhage may simulate the signs and symptoms of congenital heart disease. In addition to insufficient pulmonary blood flow and congestive failure induced by some congenital lesions, superimposed subacute bacterial infections may result in embolic infarction, multiple abscesses, and patchy pneumonia lesions.

A. *Right Aortic Arch:*

This congenital anomaly may sometimes form a vascular ring by its connection to the right pulmonary artery through a short patent ductus arteriosus or ligamentum arteriosus (Figure 1). Pressure on the right upper lobe bronchus may produce atelectasis, obstructive emphysema, or recurrent infections (tracheobronchitis or pneumonia). It may also cause the pulmonary artery to compress the anterior surface of the trachea. Pulmonary symptoms include dyspnea, cyanosis, cough, and chest pain. Head retraction and stridor may occur in infants. These symptoms may

*Presented at the Clinical Meeting, New York State Chapter, American College of Chest Physicians, February 19, 1953.

†Clinical Assistant Professor, Department of Medicine, State University of New York, College of Medicine.

be initiated later in life owing to traction caused by elongation and posterior displacement of the arteriosclerotic aorta.

X-ray studies of the barium-filled esophagus reveal compression at the level of the third intervertebral space.[2] Lipiodol studies in the lateral position delineate anterior tracheal compression just above the carina. Angiocardiography (seven second film) reveals the exact location of the vascular deformity.

When obstruction is of marked degree, the ligamentum arteriosus is divided, allowing the pulmonary artery to fall forward.[3]

B. *Double Aortic Arch:*

This anomaly occurs when both fourth branchial arteries persist. The left (anterior) arch is usually small (Figure 1). The vascular ring produces encroachment upon the trachea and esophagus, resulting in symptoms and x-ray changes similar to those listed under the right aortic arch. Complete relief is afforded by the ligation and extirpation of the left (anterior) portion of the double arch.

C. *Pulmonary Stenosis:*

Pulmonary tuberculosis has been found to occur with greater frequency in some congenital heart conditions. This is especially true of pulmonary stenosis and tetralogy of Fallot. Abbott[4] found an incidence of 36 per cent. Superimposed subacute bacterial infection on the congenital cardiac lesion with pulmonary embolization may also occur. This results in infarction, pneumonitis, or lung abscess.

The Blalock shunt operation has been employed with success, but a direct

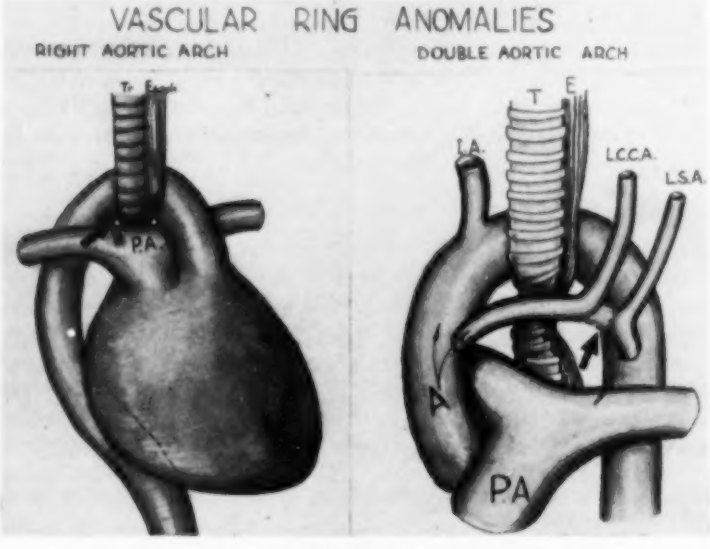


FIGURE 1

attack on the stenosing tissue by incision or punch operation is presently producing equally satisfactory results in other cases.

D. *Patent Ductus Arteriosus:*

Ordinarily, the higher pressure in the aorta allows a return flow to the pulmonary artery through this abnormal communication. Pulmonary congestion may occur eventually if the shunt is of considerable size. The most frequent complications are congestive heart failure and subacute bacterial endocarditis. The latter results in embolic infarctions of the lung. Multiple small abscesses or patchy pneumonia may ensue. Ligation of the ductus and the use of antibiotics are now producing remarkable cures.

Acute Rheumatic Fever

A. *Rheumatic Pneumonia:*

Although the incidence of rheumatic pneumonia has been reported by careful observers as varying from 2 to 15 per cent, the diagnosis is frequently overlooked. Pneumonic involvement usually occurs at the height of an attack of acute rheumatic fever. The pathologic changes consist essentially of irregularly scattered areas of hemorrhagic consolidation. Cough and sputum are not prominent features. The diagnosis rests on finding signs of transitory and migratory pulmonary exudates during the course of acute rheumatic fever.[5] This is demonstrable on serial x-ray studies (Figure 2). Part of one lobe may be involved or the inflammatory process may extend to all the lobes. The lesions clear rapidly following the use of ACTH or cortisone although this is difficult to evaluate because of the migratory nature of the lesions.

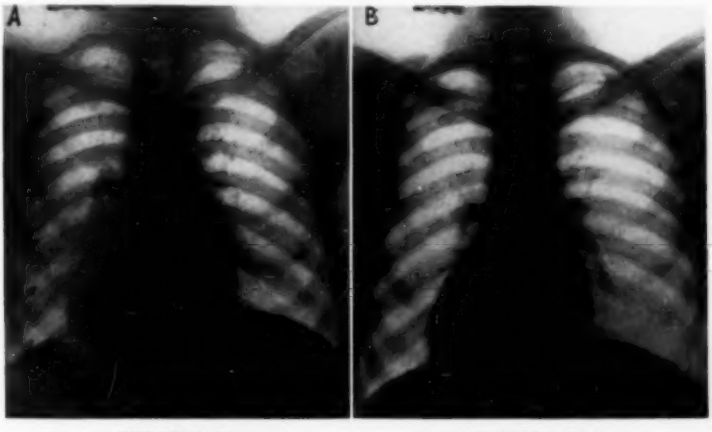


FIGURE 2A FIGURE 2B

Figure 2: Rheumatic Pneumonia. (A) Irregularly scattered areas of soft infiltrations throughout both lower lung fields, more marked on the left side. Onset of pneumonic involvement occurred the previous day.—(B) Marked diminution in extent and intensity of the infiltrations the following day illustrating the transitory nature of the exudates.

Virus pneumonia may be differentiated by the absence of other rheumatic fever manifestations, low white count, persistence of hacking cough, platelike areas of atelectasis radiating from the hilium which are not transitory, and the demonstration of cold hemagglutinins in the blood.

B. *Rheumatic Pleurisy:*

Pleurisy is probably another manifestation of acute rheumatic fever owing to inflammation of the subendothelial connective tissue. Although acute fibrinous or serofibrinous pleuritis is recognized clinically in only 5 to 15 per cent of all cases of acute rheumatic fever, they are found in half the cases at autopsy. They may occur on either or both sides and usually follow lung or pericardial involvement.[5] Characteristically, the initial severe inspiratory pain and friction rub disappear within several days as effusion accumulates. Routine roentgenograms demonstrate fluid in a high percentage of cases. Aspiration is seldom required. A clear or cloudy serofibrinous exudate occurs but it may appear hemorrhagic, possibly due to the presence of pulmonary infarction. Although the fluid is rapidly absorbed, adhesions develop occasionally. There may be pleuropericardial adhesions which give the cardiac silhouette a scalloped appearance or partially obliterate the pleural space.

Mitral Valvular Disease

A. *Chronic Congestive Failure:*

Mitral valvular lesions, especially stenosis, may account for the early occurrence of pulmonary congestion in many cases. As a result of chronic congestive heart failure, the lungs become firm, dense, and red-brown in appearance. There is interstitial edema, increased collagen, and thickening of the capillary basement membrane. These changes thicken the alveolar wall and interfere with oxygen exchange. They also may produce an inelasticity of the lung tissue which interferes with lung expansion.

Dyspnea and orthopnea are major symptoms. Cyanosis may also be evident. Hemoptysis occurs in 10 per cent of cases of mitral stenosis. Although it may appear at any time during the course of the disease, it usually denotes an advanced degree of stenosis with increasing pulmonary congestion. The blood lost is usually small but indicates a dire prognosis. Cough is commonly present, and when productive, the sputum is mucoid, but may be blood streaked or frankly purulent due to secondary bronchopulmonary infection.

B. *Acute Pulmonary Edema:*

Acute pulmonary edema may occur in mitral stenosis and other valvular lesions even when regular sinus rhythm exists. It usually follows severe exertion, an operation, pregnancy, rapid digitalization, or paroxysmal tachycardia. Attacks are precipitated by the added strain on the right heart in the presence of pulmonary congestion. Treatment includes digitalization, morphine and atropine, oxygen, mercurials and antifoaming

agents.[6] Subsequently, valvuloplasty may be indicated. Remarkable results have already been reported by many surgeons.

C. *Rupture:*

Rupture of a papillary muscle or chordae tendinae rapidly results in pulmonary congestion. This may be caused by superimposed subacute bacterial endocarditis, coronary thrombosis, or trauma.

D. *Pulmonary Infarction:*

The effects of pulmonary infarction are discussed elsewhere. Suffice it to say that this serious complication may result from the discharge of clots from the right auricle during auricular fibrillation. It is important not to overlook other major causes such as peripheral or pelvic venous thrombosis. Early treatment of the primary heart condition and the use of anticoagulants have greatly reduced morbidity and mortality. Amputation or ligation of the auricular appendage is presently employed with success in cases with recurrent embolization (Madden).

Bacterial Endocarditis

The acute and subacute forms of bacterial infections of the valvular and mural endocardium may be caused by many microorganisms. However, the nonhemolytic streptococcus accounts for 95 per cent of all cases. In order for emboli to reach the lungs the right heart must obviously be affected. Septal defects, pulmonary or tricuspid stenosis, patent ductus arteriosus, tetralogy of Fallot, or other combined congenital lesions may also provide the necessary focus.

Pulmonary emboli and infarctions, congestion, bronchopneumonia, or lung abscesses may be encountered. The infarctions usually are too small to be visualized on the x-ray film. Pleural effusions or hemorrhages are not uncommonly found. Emboli in pulmonary arterial branches may result in arteritis or mycotic aneurysm. Symptoms include cough, chest pain, and dyspnea. Bloody expectoration may be present. Antibiotics are effective in most cases when properly selected and when administered in adequate dosage.

Acute Nonspecific Pericarditis

The pleura is commonly involved in acute pericarditis of nonspecific origin but is frequently overlooked. The recurrent nature of this disease is emphasized.[7] Cases are now on record in which the number of recurrences has ranged from two to 19. A pleural lesion must be suspected when the clinical and laboratory findings of acute nonspecific pericarditis are accompanied or followed shortly by the onset of a pleural friction rub on either or both sides which may last for days or weeks. This may progress to a pleural effusion of varying degree (usually small in amount) and, finally, progressive pleural thickening. Large amounts of pericardial effusion may result in extensive compression atelectasis (Figure 3). The aspirated fluid is exudative and nonbloody, and may be bilateral.[8] Pleural

fluid is demonstrable by roentgenogram. Persistence of fever, following improvement of the pericarditis and invariable recovery further suggest the presence of pleural involvement. Pulmonary involvement is uncommon. The condition is differentiated from primary atypical pneumonia with secondary pericarditis by the absence of initial cough, leucocytosis and absence of lung findings on x-ray film. Results with aureomycin, chloromycetin and terramycin have been equivocal thus far.

Chronic Constrictive Pericarditis

Chronic constrictive pericarditis is a dense fibrous thickening of the pericardium which may cause compression of the heart and which interferes with normal filling. It is characterized clinically by a small quiet heart, elevated venous pressure and ascites.

Although tuberculosis is the commonest cause in cases with proved etiology, this disease accounts for only 15 per cent of all cases. Thus, evidence of active or inactive pulmonary tuberculosis may be found in an occasional case of chronic constrictive pericarditis. Polyserositis due to tuberculosis (Concato's disease) has never been proved to be a distinct clinical entity.

The lungs usually do not reveal significant congestion or fibrosis. However, pleural adhesions or effusions are fairly common. When the constricting pericardial scar is localized mainly over the left auricle, relaxation and filling of this chamber may be seriously interfered with. Constriction around the pulmonary vein orifices may result in marked pulmonary engorgement.[5] Dyspnea may be due to extensive pleural effusions, pulmonary congestion, or decreased vital capacity owing to marked elevation

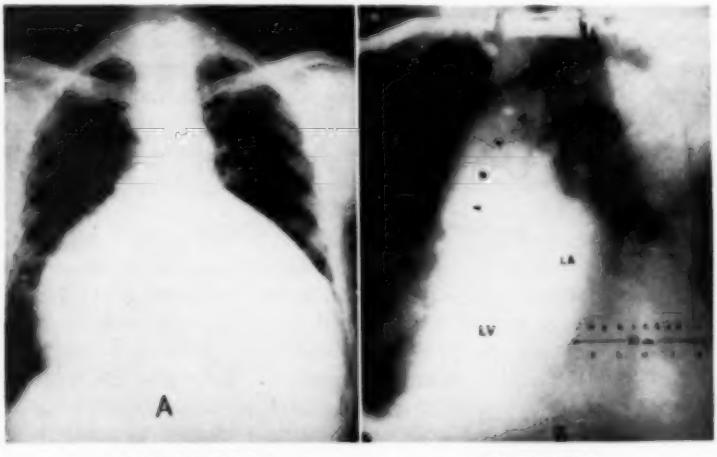


FIGURE 3A FIGURE 3B

Figure 3: Massive Pericardial Effusion producing extensive compression of lung tissue. (A) PA view shows marked water bottle appearance.—(B) Angiocardiogram of LAO view shows extent of fluid posteriorly with contrast media in left heart and aorta.

of the diaphragm by ascites. The vital capacity was reduced up to 68 per cent of normal in the cases reviewed by Stewart and Heuer.[9]

Dramatic improvement occurs following surgical removal of the constricting scar tissue. Streptomycin, PAS, and isonicotinic acid derivatives are of value in the treatment of active tuberculous lesions.

Syphilis

Saccular aneurysms may reach alarming proportions and may produce symptoms and signs of compression of the lungs, bronchi, and other structures depending on the direction and extent of their dilatation (Figure 4). Aneurysms of the arch are most important because of their greater proximity to respiratory structures. Pulmonary signs of atelectasis, bronchiectasis, and secondary infection may result. Tracheal tug may be elicited and left recurrent laryngeal nerve compression may result in hoarseness or aphonia. Phrenic nerve involvement may produce paralysis of the diaphragm, thereby interfering with oxygenation.

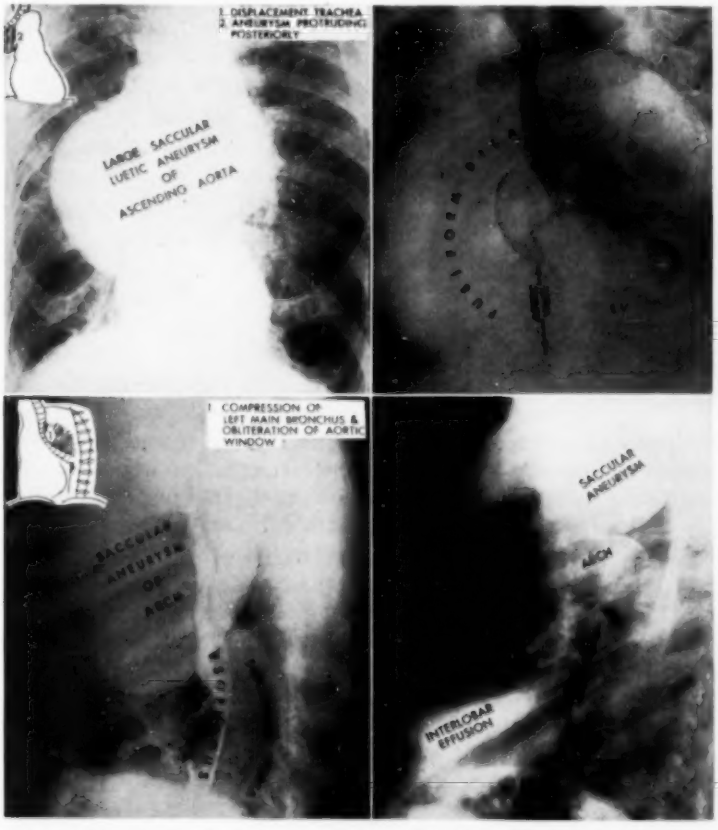

1. DISPLACEMENT TRACHEA
2. ANEURYSM PROTRUDING POSTERIORLY
LARGE SACCULAR LUETIC ANEURYSM OF ASCENDING AORTA
1. COMPRESSION OF LEFT MAIN BRONCHUS & OBLITERATION OF AORTIC WINDOW
SACCULAR ANEURYSM
AORTA
INTERLOBAR EFFUSION

FIGURE 4: Effect of cardiovascular syphilis on the respiratory system.

The most important of these complications is *atelectasis*. Unless the lesion is sufficiently extensive, tactile fremitus is frequently a misleading sign because of the failure of a wide area of tactile sense of the hands to localize properly small lesions or extensive early ones. An ordinary 100 cc. Erlenmeyer flask or 75-watt electric bulb applied lightly to the chest wall may elicit minor changes more satisfactorily.[10] Diminished breath sounds and altered resonance on percussion may be noted. Bronchiectasis may ensue from lack of drainage and infection induced by bronchial compression.

Endobronchial tumors and other lesions must be differentiated occasionally. Bronchography may reveal the true cause of localized obstructions or distortions of the bronchial tree. Tomography may exclude endobronchial tumor by delineating cavitation within the aneurysmal mass. This is unreliable when the aneurysm is clotted. Kymography may show typical expansile pulsations when the aneurysm is unclotted. Further differentiation of adenoma, carcinoma, and inspissated mucous or granulomatous tissue rarely requires bronchoscopy, biopsy, or Papanicolaou staining of sputum for tumor cells. Serologic tests are positive in approximately 85 per cent of cases. Calcification in the wall of the ascending aorta (LAO view) is found in approximately half of all cases of luetic aortitis.

Antibiotics now have a definitely established position in the treatment of cardiovascular syphilis. Aneurysms have been wired and electrocoagulated, or surrounded by Polythene Cellophane (PT 300) in order to shrink them or prevent further expansion with rupture.

Myocardial Infarction

A number of pulmonary complications is possible in patients suffering from myocardial infarction. The following lesions must be considered when lung findings appear following this condition.

A. *Pulmonary Edema:*

This serious pulmonary complication is due to acute ventricular failure, since the left ventricle is most commonly affected by infarction. It may be the dominant manifestation of an acute myocardial infarction appearing suddenly within hours to days following a coronary artery occlusion.

Symptoms include thoracic oppression, dyspnea, orthopnea. Cough may be a prominent feature. The attack may be characterized by episodes of paraxysmal nocturnal dyspnea with wheezing respirations and rhonci. Mild pulmonary congestion is common when the dominant manifestation is pain, shock, or congestive heart failure. Basal rales are heard in such cases, especially on the right side. Edema may become more severe with noisy respirations and the appearance of copious white or pink foam. In advanced cases it may pour out of the oronasal passages and bubbling rales are audible up to the apices. Digitalis preparations, oxygen, morphine and atropine, diuretics, anticoagulants, and antifoaming agents are employed in the treatment of acute pulmonary edema.[6]

B. *Atelectasis:*

It is very common to find a localized patch or patches of crepitant rales at the left lung base, coinciding with x-ray film demonstration of plate-like areas of atelectasis. However, this is found so frequently early in the attack that it is considered normal by Wolff and not necessarily indicative of congestive failure, pulmonary infarction, or infection.[11]

An area of dullness and bronchial breathing without temperature elevation usually indicates the presence of atelectasis. Oxygen and expectorants may be of value in therapy. Rebreathing is obviously contraindicated in cases following myocardial infarction.

C. *Pneumonia:*

Pneumonia is rarely associated with acute myocardial infarction and yet this diagnosis is made with alarming frequency and the patient treated as such. The possibility of other lesions such as localized pulmonary edema, pulmonary infarction, or atelectasis must be investigated. When there is leucocytosis, hyperpyrexia, and mucopurulent sputum, in addition to lung signs, a therapeutic trial with an antibiotic is indicated.

D. *Localized Pulmonary Edema:*

This complication is not uncommon in acute myocardial infarction and is usually bilateral. The condition is commonly confused with pneumonia or pulmonary infarction. In addition to dullness or flatness and bronchial breathing, a shower of fine inspiratory rales is frequently heard. The clinical course is usually severe with frank hemoptysis, marked pyrexia, and leucocytosis. Signs of gross congestive failure may ensue in some patients. The x-ray film is diagnostic.[11]

E. *Pulmonary Infarction:*

It is well to remember that emboli to the lung may occur following auricular fibrillation and peripheral venous thrombosis as well as right-sided mural thrombosis due to myocardial infarction. Emboli may enter any part of the pulmonary artery branches, but most commonly proceed to the right base. The sudden onset of chest pain, cough and bloody expectoration usually heralds this complication. Signs include localized crepitant rales, dullness and bronchial breathing. Pleural pain is present in half the cases but a rub is diagnosed in only 10 per cent of the cases.[12] Effusions are usually too small in amount to be recognized clinically. When present, fluid may be clear or sanguinous. On rarer occasions, large recurrent effusions may dominate the clinical picture, but they seldom require aspiration. The icterus index may be slightly elevated on the second or third day. The electrocardiogram is diagnostic (acute cor pulmonale) in a large percentage of the cases, but x-ray investigation is usually disappointing. Immediate anticoagulant therapy is indicated. Venous ligation must be considered when embolization from the peripheral or pelvic veins is suspected.

Dissecting Aneurysm

There has been a marked improvement in the recognition of dissecting aneurysms during the last decade (Figure 5). This has been due to an awareness of the disease on the part of most clinicians. Efforts at limiting the pathology to a single factor have been generally unsuccessful although medial necrosis is recognized as the most important pathologic factor.[1] Pulmonary symptoms are rare in the absence of rupture but signs include cough and hemoptysis. When not instantly fatal, various clinical syndromes may appear depending on the site and extent of dissection or rupture.

Twenty per cent of all dissecting aneurysms rupture into the left pleural cavity and present characteristic signs of chest fluid.[13] Fluid in the left pleural cavity due to such ruptures must be differentiated from that due to circulatory failure (which seldom affects the left side alone), malignancy of the pleura, and Meig's syndrome. Aspirated bloody fluid is highly significant for dissection. The presence of malignant cells and tubercle bacilli must be investigated. Ruptures into the right pleural space, mediastinum and other structures have been described on rare occasions. Massive hemoptysis may indicate rupture directly into the trachea, bronchi or lung.

Blood replacement and pleural aspiration are indicated. The recent availability of enzymatic agents (Tryptar and Streptokinase) now makes it possible to liquify blood clots prior to aspiration. Surgical repair of the site of rupture may be attempted by employing gelatin sponge cuffs or by applying Polythene Cellophane (PT 300).

Neoplasms

Primary and secondary tumors of the heart are relatively rare. We are concerned presently only with primary neoplasms. They occur approximately once in every 2,000 cases that come to autopsy.[14] The frequency of types has been reported in the following order: myxoma, sarcoma

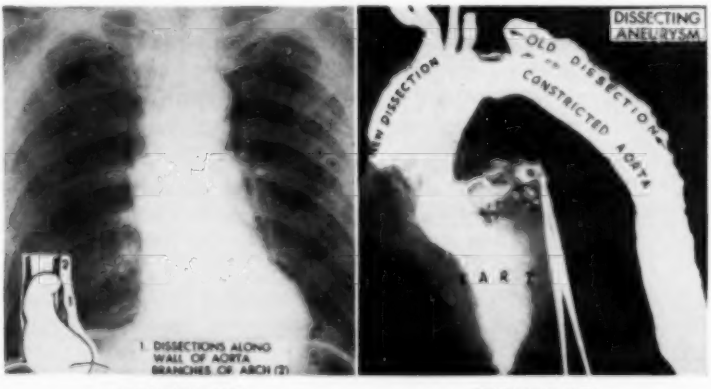


FIGURE 5A FIGURE 5B

Figure 5: Dissecting Aneurysm. Eventual rupture into the left pleural space with massive hemothorax. (A) Roentgenogram prior to rupture.—(B) Injected specimen.

rhabdomyoma, fibroma, lipoma, angioma, cystoma, papilloma, teratoma, and epicardial epithelioma. Any heart chamber may be the site of neoplasm, but the right side is more commonly involved. Therefore, pulmonary metastases from primary cardiac malignancies are frequently found.

Diagnosis of a primary lesion should be suspected in cases of heart disease of undetermined etiology when (1) roentgenogram shows an unexpected or bizarre heart size or shape, (2) there are progressive electrocardiographic changes otherwise unexplained, and (3) pericardial aspiration reveals red cells and tumor cells. Pedunculated intracardiac tumors may produce intermittent obstruction of valve orifices and simulate valvular lesions. The subsequent appearance of metastatic pulmonary lesions with or without pleural involvement should further suggest the possibility of malignancy. This is especially true when pleural transudates also contain tumor cells or when stained bronchial secretions reveal tumor cells of non-carcinomatous origin.

Treatment may be effective when the tumor is benign and pedunculated. Such tumors have been removed from within the heart (Beck, Bailey). Radiotherapy and chemotherapy have produced no known cures thus far, although life may be prolonged in some cases of malignant lymphoma.

Chronic Cor Pulmonale

Chronic cor pulmonale is a term applied to hypertrophy of the right ventricle, with or without congestive heart failure. Despite a varied etiology which includes a number of pulmonary, cardiac and vascular disturbances, increased resistance and pressure in the pulmonary circuit is the basic mechanism.[7] Since we are dealing with the pulmonary complications of primary heart disease, the pulmonary factors will not be considered. However, it is significant that when congestive failure supervenes, other pulmonary findings become superimposed on the underlying lung disease process (e.g., pulmonary emphysema and other bronchopulmonary diseases).

Systemic hypertension, rheumatic valvular lesions, and other causes of left-sided failure may eventually result in pulmonary hypertension. Congenital cardiac lesions with an arteriovenous shunt (patent ductus arteriosus, septal defects, aberrant pulmonary veins) may be at fault. Rupture of an aortic aneurysm into the pulmonary artery or rupture of an aneurysm of the right sinus of Valsalva may produce a similar effect. Various diseases of the pulmonary arteries may also be involved. Kyphoscoliosis, funnel chest, and other chest deformities may similarly result in hypertrophy and dilatation of the right ventricle. It is the consensus of opinion that the syndrome occurs in about 75 per cent of cases of severe kyphoscoliosis. These deformities may also produce compression atelectasis or secondary emphysema in addition to bronchopulmonary infections.

The diagnosis of chronic cor pulmonale is based upon the recognition of the underlying causative factor and the discovery of right ventricular enlargement with or without evidence of failure. Right-sided failure is recognizable by the presence of hepatomegaly, dependent edema, elevated venous pressure, and prolonged arm to lung circulation time. It is important

to remember that dyspnea and cyanosis are usually due to the underlying lung or heart disease, but may be aggravated in the presence of congestive failure.

Roentgenologic studies show (a) an exaggeration of the hilar markings due to enlargement of the pulmonary artery and its major branches, (b) enlargement of the right ventricular outflow tract in the LAO view

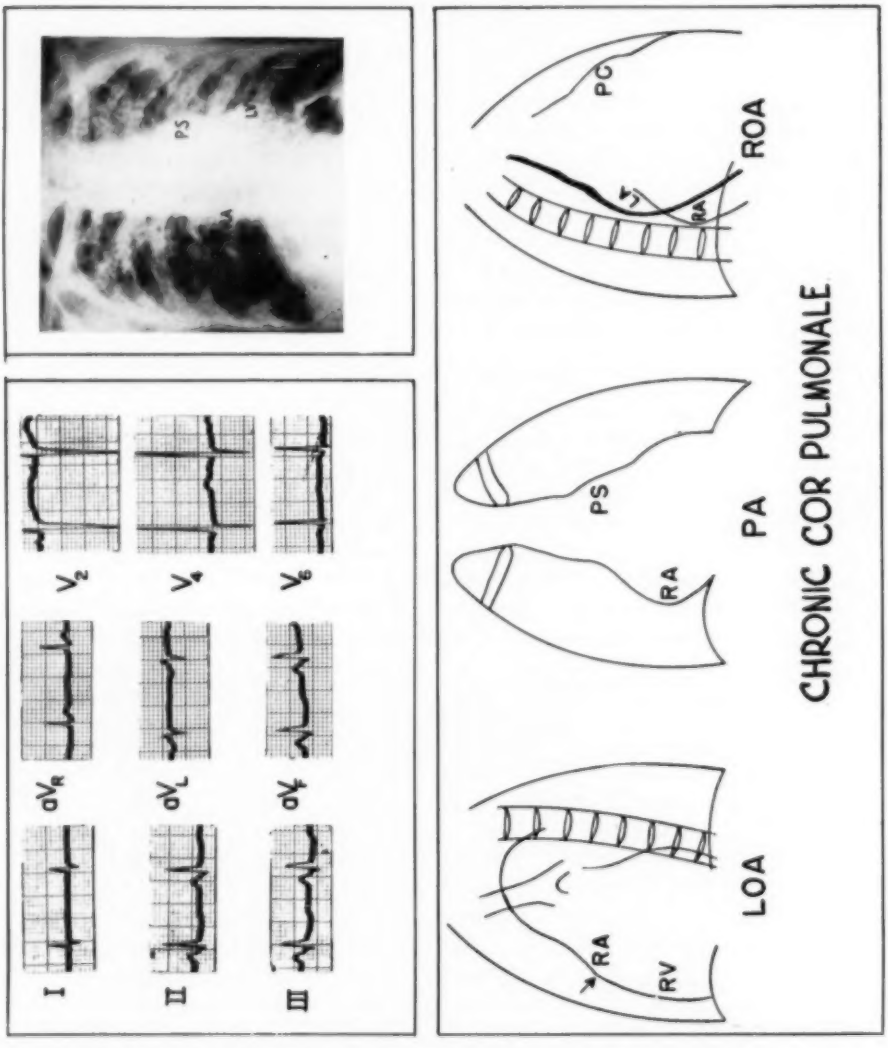


FIGURE 6: Chronic Cor Pulmonale. Electrocardiogram and roentgenogram of PA view showing pulmonary hypertension (prominent pulmonary segment and enlarged right auricle) secondary to extensive pulmonary tuberculosis. Diagrams of cardiac outlines in the standard views.

as indicated by the posterior displacement of the interventricular groove, and in the right lateral position by the encroachment of the right ventricle on the retrosternal space, and (c) prominence of the pulmonary segment in the PA view. When decompensation occurs, (a) the right auricle may become enlarged, (b) there is enlargement of the right ventricular inflow tract as well, (c) the transverse diameter of the heart is further increased in size, (d) the lower lung fields reveal congestive changes or fluid (Figure 6). Electrocardiograms show a progressive right ventricular strain pattern.

Treatment must be directed at the causative lesion. In many disorders, such as kyphoscoliosis, it is usually unsatisfactory. In others, such as patent ductus arteriosus, early surgical intervention may result in complete relief. When frank heart failure develops, oxygen therapy is indicated. Digitalis produces equivocal results in this type of failure but should be given a therapeutic trial. Venesection may prove beneficial in the presence of high plasma and cell volumes. Antibiotics are indicated in the presence of underlying or intercurrent bronchopulmonary infections. Morphine is definitely contraindicated since it depresses respiratory activity.

SUMMARY

1) The appearance of pulmonary lesions during the course of many heart diseases must be evaluated carefully for proper diagnosis, prognosis and therapy.

2) Pulmonary complications may appear following certain congenital cardiac defects, acute and chronic inflammations of the heart and aorta, degenerative lesions of the coronary arteries and aorta, primary neoplasms of the heart and chronic cor pulmonale.

3) Cardiovascular disease may cause tracheal or bronchial compression, marked hypertrophy of bronchial arteries and veins leading to hemoptysis, pulmonic venous, pulmonic arterial, or combined hypertension, pulmonary emboli and infarcts, and pleural effusions. Heart disease predisposes the respiratory system to edema, bronchospasm and bronchial hypersecretion of mucus, and to various infections.

4) The pathogenesis, differential diagnosis, and therapy of these respiratory disorders due to cardiovascular disease have been presented.

RESUMEN

1) La aparición de lesiones pulmonares durante la evolución de muchas afecciones del corazón, debe ser considerada con cuidado para hacer un diagnóstico adecuado así como pronóstico y su terapéutica.

2) Pueden aparecer complicaciones pulmonares en ciertas malformaciones cardiacas congénitas, inflamaciones agudas y crónicas del corazón y de la aorta, lesiones degenerativas de las coronarias y de la aorta, neoplasias primarias del corazón y en el cor pulmonale crónico.

3) La enfermedad cardiovascular puede causar compresión traqueal y bronquial, marcada hipertrofia de las arterias bronquiales y de las venas que pueden provocar hemoptisis, hipertensión de las venas y arterias pulmonares o de ambas, embolia pulmonar. El padecimiento pulmonar pre-

dispone el aparato respiratorio al edema, broncoespasmo e hipersecreción mucosa así como a varias infecciones.

4) Se presentan consideraciones sobre la patogenia, el diagnóstico diferencial y el tratamiento de estos trastornos respiratorios debidos a la enfermedad cardiovascular.

RESUME

1) Il est nécessaire d'évaluer avec soin les caractères des altérations pulmonaires au cours de l'évolution de nombreuses affections cardiaques. Ce n'est qu'ainsi qu'on pourra en établir correctement le diagnostic, le pronostic et le traitement.

2) On peut voir apparaitre des complications pulmonaires dans les cas suivants: certaines anomalies cardiaques congénitales, lésions inflammatoires aigues ou chroniques du coeur ou de l'aorte, lésions digénératives des artères coronaires et de l'aorte, cancer primitif du coeur et coeur pulmonaire chronique.

3) Les affections cardio-vasculaires peuvent être la cause de troubles divers, compression trachéale ou bronchique, hypertrophie des artères et des vaines poumonaires, pouvant entrainer l'apparition d'hémoptysies, hypertension du système pulmonaire artériel ou veineux ou des deux systèmes à la fois, infarctus et embolies pulmonaires, épanchements pleuraux. Les affections cardiaques en outre sont, pour l'appareil respiratoire, une cause prédisposante à l'oedème, au bronchospasme, à l'hypersécrétion bronchique de mucus et aux infections diverses.

4) L'auteur expose la pathogénie, le diagnostic différentiel, et le traitement de ces atteintes respiratoires consécutives aux affections cardiovasculaires.

REFERENCES

1 Reich, N. E.: "Diseases of the Aorta," C. C. Thomas, Springfield, Ill., 1949.
2 Neuhauser, E. B. D.: "Roentgen Diagnosis of Double Aortic Arch and Other Anomalies of the Great Vessels," *Am. J. Roentgenol.*, 56:1, 1946.
3 Gross, R. E.: "Surgical Treatment for Abnormalities of the Heart and Great Vessels," C. C. Thomas, Springfield, Ill., 1947.
4 Abbott, M. E.: "Atlas of Congenital Cardiac Disease," *Am. Heart Assn.*, N. Y., 1936.
5 Reich, N. E.: "Protean Manifestations of Acute Rheumatic Fever," *Am. Practitioner*, 12:645, 1947; "Acute Rheumatic Fever in Uncommon Sites," *Am. Practitioner*, 2:328, 1951.
6 Reich, N. E.: "The Use of 2-Ethlyhexanol in Acute Pulmonary Edema," *Dis. of Chest*, 23:43, 1953; "A New Therapy for Acute Pulmonary Edema," *N. Y. State J. Med.*, 52:2647, 1952.
7 Tomlin, C. E., et al.: "Recurrent Nature of Acute Benign Pericarditis," *J.A.M.A.*, 149:1215, 1952.
8 Reich, N. E.: "The Uncommon Heart Disease," C. C. Thomas, Springfield, Ill. (In press).
9 Stewart, H. J. and Heuer, G. J.: "Chronic Constrictive Pericarditis: Dynamics of Circulation and Results of Surgical Treatment," *Arch. Int. Med.*, 63:504, 1939.
10 Reich, N. E.: "Method of Applying Flask to Chest in Tactile Fremitus," *N. Y. State J. Med.*, 39:1654, 1939.
11 Wolff, L.: "Diagnostic Implications of Pericardial, Pleural and Pulmonary Involvement in Cardiovascular Disease," *N. Eng. J. Med.*, 244:965, 1951.
12 Sagall, E. L., et al.: "Clinical Syndrome in Patients with Pulmonary Embolism," *Arch. Int. Med.*, 76:234, 1945.
13 Reich, N. E.: "Dissecting Aneurysm of the Aorta: A Clinicopathologic Correlation of 19 Cases," *Clinics*, 3:346, 1944.
14 Lymburner, R. M.: "Tumors of the Heart: Histopathological and Clinical Study," *Canad. M. A. J.*, 30:368, 1934.

Sarcoma of the Lung*

THEODORE H. NOEHREN, M.D., F.C.C.P. and FRANK W. McKEE, M.D.
Buffalo, New York

Primary sarcoma of the lung is a rare entity. Some authors[1,2] even deny its existence. Mallory,[3] in 1936, listed it among the rarest of tumors, reporting the first one in over 8,000 autopsies at the Massachusetts General Hospital. Since then three more cases have been published from that hospital. One case of primary sarcoma of the lung was found in 7,272 autopsies, an incidence of 0.014 per cent from the University of Kansas Hospitals.[4] Our surveys of all admissions at the Mayo Clinic and the University of Rochester Strong Memorial Hospital revealed only one case at each institution prior to 1949.

There was a time, however, when this sarcoma was considered the most common primary pulmonary malignancy. That was in 1903 when primary malignancy of the lung of any type was "a rare disease."[5] The transition to our present concept of malignant tumors of the lung bears an important relation to our clinical impressions of these entities, for, while the diagnosis of sarcoma in most of these earlier cases has been questioned or found incorrect, the clinical symptoms of these same cases are retained as diagnostic criteria for this tumor.

The clinical concept of primary sarcoma of the lung as it is described in the textbooks therefore is confusing. Many texts contain no discussion of it at all. In others, it is characterized as a lesion "in young people under 40[6,7] . . . with extremely rapid spread . . . giving rise to multiple and widely diseminated secondary deposits in the lung[8] . . . with characteristic grass-green sputum[9] . . . all of which needs revision if we may judge by our present material on the subject.

Ewing[10] pointed out that most of the cases in the early literature concerned "lesions which were associated with tuberculosis, syphilis, or chronic suppuration, and others appear to have been forms of productive or organizing pneumonia. Boyd[11] suggests that many of the supposed cases that were described undoubtedly were examples of the anaplastic forms of carcinoma in which the cells may be round, spindle-shaped, or oat-shaped.

Finally, the "blind-men-and-the-elephant" deductions of the "one case" reports have added their confusion to the clinical concept of sarcoma of the lung. They, together with the slow metastatic process to the lung of sarcoma from elsewhere in the body (osteogenic, etc.), make premature the deductions from some of the current reports of surgically removed chest tumors. Many lesions that are considered primary sarcoma, in time prove metastatic.

We have assembled from the medical periodicals since 1912 a group of 34 cases of primary sarcoma of the lung, to which we will add one case.

*Presented at the 19th Annual Meeting, American College of Chest Physicians, New York City, May 28-31, 1953.

This series does not represent all the published reports claiming to this diagnosis. Only cases with an adequate follow-up or post-mortem study, and with a description of the tumor and its microscopic sections which allow critical evaluation, have been included.

The case we studied, M.V. (SMH 101300), was a 61 year old white woman, who was admitted with a chief complaint of "shortness of breath," of two years duration. In the three months prior to admission this became more severe, although she remained up and about, continuing with her housework until several weeks before hospitalization. At that time, she noted orthopnea, except when lying on her right side. Five days prior to admission, there was one transient episode of ankle edema. There was no precordial or chest pain.

She noted a dry, nonproductive cough for 40 years. There were annual winter episodes of "pleurisy" with pain along the left costal margin and in the left shoulder blade until about 38 years prior to admission. In the past 10 years she had rare attacks of heart fluttering, noted chiefly in the neck and radial pulses. These attacks appeared when she was tired, lasted several days, and made her feel weak. She also complained of associated gaseous indigestion and severe epigastric pain radiating to the back and shoulder blades, lasting as long as one hour at a time. Her physician had considered these gall-bladder attacks. Nocturia, 7 to 8 times a night had been present as long as the patient could remember. There were no other urinary symptoms.

Past History: She had the usual childhood diseases. A pelvic "tumor" had been surgically removed 19 years previously.

Family History: Her mother died of cancer at the age of 55 years. Her father died at 55 years of heart trouble. Two sisters had died of tuberculosis.

Physical Examination: The temperature was 37.8 degrees C., pulse 88, and respirations were 22. The blood pressure was 180 mm. systolic and 70 mm. diastolic. She was an acutely ill white woman, appearing somewhat older than her stated age. Her respirations were rapid, shallow, and gasping in quality. Her eyes appeared sunken, and her cheeks thin and pale. Her skin was dry, and loosely fitting, showing evidence of subcutaneous tissue loss. Examination of the head was negative. The eyes showed marked arcus senilis, with regular and equal pupils which reacted to light. The media were clear. Extra-ocular movements were normal The optic disks appeared normal, but the arterioles were markedly narrowed and the tortuous with an increased light reflex. There was minimal arterio-venous compression. Her hearing was poor and bone conduction exceeded air conduction. Examination of the nose was negative. Complete edentia was evident, and the tongue was smooth and reddened. Examination of her neck was not remarkable. The left lobe and isthmus of the thyroid were enlarged, with some palpable nodules, but without thrill or bruit. The diameter of the thoracic cage was increased, and there was conspicuous prominence of the right second and third ribs at the costo-chondral junction. Superficial veins were prominent over both breasts. The left lung was clear to auscultation and percussion. The right chest, however, was flat to percussion with breath sounds, tactile fremitus, and whispered voice all absent below the mid-scapular region posteriorly, and over the lower right axilla. Egophony was noted over this same area. The heart was not enlarged. The cardiac rhythm was regular, with sounds of good quality and no murmurs were detected. P_2 was greater than A_2. The peripheral vessels were thickened and nodular. No abnormality was noted about the abdomen. Neurologic reflexes were equal and active throughout.

Laboratory Findings: Hematology-erythrocytes: 4,800,000, hemoglobin: 14.0 gms., leukocytes: 6,250 with 70 per cent polymorphonuclears, 24 per cent lymphocytes, 5 per cent monocytes, 1 per cent basophils. The blood smear was not remarkable.

Urine: A trace of albumin was noted. Microscopic examination revealed no

casts or cells. Non-protein nitrogen determination was 28 milligrams per cent. There was a question of some myocardial damage on the electrocardiogram recording. The Wasserman test was negative. Roentgenogram of the chest showed a density at the right base (Figure 1).

Hospital Course: Shortly after admission 850 cc. of cloudy yellow fluid was removed from the right chest by thoracentesis. Two days later aspiration produced 950 more ccs. of similar fluid. Histological examination of the sediment revealed only chronic inflammatory cells. (The pleural fluid culture developed no growth. The fluid contained 4.8 grams per cent protein and had a specific gravity of 1.018. Sections of the centrifuged pleural fluid sediment showed many lymphocytes and round cells with dark staining nuclei but no definite diagnosis was made.) Following thoracentesis the patient complained of some pain in her right chest. A loud to-and-fro leathery friction rub was heard over the upper right chest. Nine days later a third thoracentesis was attempted and only blood was obtained. A second attempt on the same day produced 350 ccs. of frankly bloody fluid, which was removed because of the respiratory difficulty. Two days later another 600 ccs. of frankly bloody fluid was removed. She became steadily weaker and more dyspneic. The heart rate became rapid but remained regular. Digitalization was attempted 15 days after admission but without benefit. She declined rapidly in the last 10 days, the dyspnea was worse, and a high fever developed. Terminally she complained of pain in her left lower chest. She finally died 25 days after admission.

Post Mortem Examination

The autopsy (SMH. A-3120) was performed four hours after death by Dr. W. B. Hawkins. The body was emaciated and the only external finding of note was a low midline abdominal scar. The peritoneal cavity contained no free fluid and fibrous adhesions were present beneath the scar. The uterus, tubes and ovaries were absent. The left pleural cavity contained no free fluid. The right pleural cavity also contained no free fluid, but the lower lobe was tightly adherent to the lateral chest wall.

Heart: Weighed 330 grams. The chambers were of normal size with a grey friable

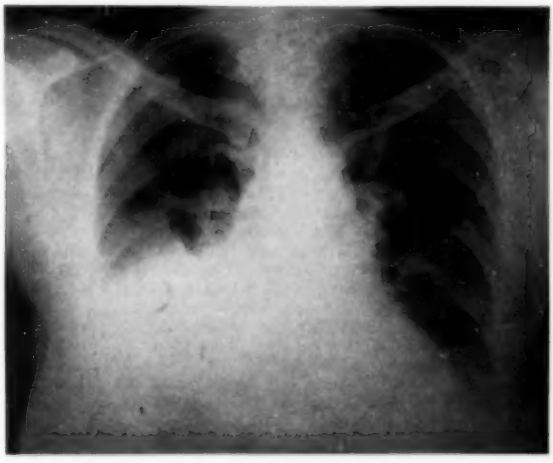


FIGURE 1: ***Chest Roentgenogram***

This was interpreted as indicating pleural effusion, pneumonia, or pulmonary malignancy in the right lower lobe.

mural thrombus present in the apex of the right ventricle. The underlying myocardium was grey and scarred. A few friable mural thrombi were also present in the auricle. The coronary vessels were sclerotic and narrow but were patent throughout.

Lungs: The left lung weighed 450 grams and the right 990 grams. The left lung

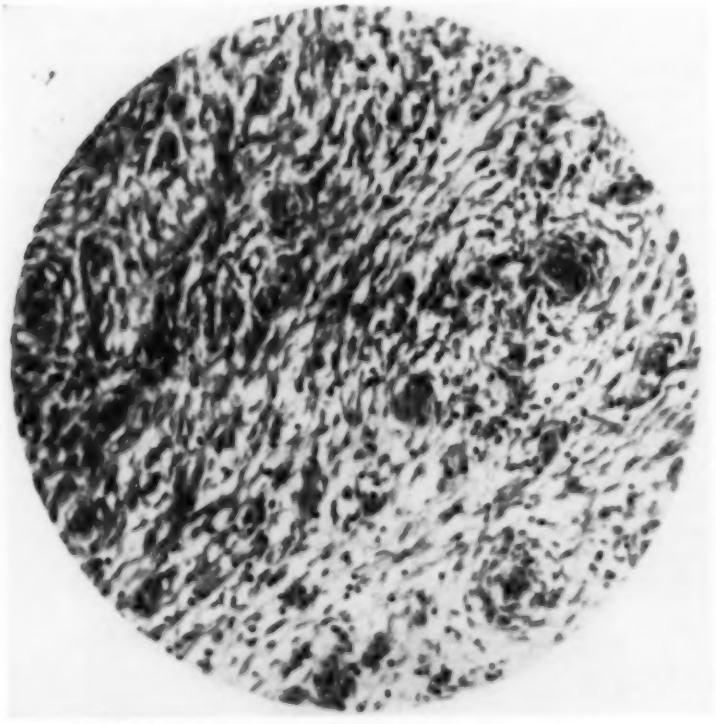


FIGURE 2

In areas the tumor resembled a simple fibroma with interlacing cell structure but elsewhere it was more active. Mitoses were uncommon. The margin was rather well demarcated with finger-like projections into the normal parenchyma. At the margin were identifiable bronchioles encompassed by tumor cells, but otherwise the tumor completely obliterated the normal lung structure. Metastatic growths of similar tissue was found in sections from the left upper lobe. The pleura overlying the tumor was covered with fibrinous exudate. Thrombi were present in many arteriole branches in sections showing the infarcts. The margin of the older infarct consisted of necrotic shadows of lung parenchyma while the underlying tissue was granular and amorphous and contained many colonies of bacteria and both intact and degenerated polymorphonuclear cells.

Sections of the heart showed organizing mural thrombi overlying scarred and organizing defects in the myocardium. The central areas of the liver were undergoing early necrosis with accumulations of acute inflammatory cells and some loss of structure.

The final diagnoses were: Spindle cell sarcoma of the lung, right lower lobe, with metastases to left upper lobe. Old and recent myocardial scarring with mural thrombi of right auricle and ventricle. Thrombosis of left iliac artery. Multiple pulmonary emboli with recent hemorrhagic and older infected necrotizing infarctions of the left lower lobe. Fibrinous pleurisy. Central necrosis of the liver. Emaciation. Chronic cholecystitis and cholelithiasis.

was firm with granular areas on the pleural surface of the lower lobe. The pulmonary arteries contained greyish friable thrombi in the main branches and in the smaller rami of the lower lobe. An area of infarction measuring 6 cms. in diameter with necrosis and softening of the tissue and resultant cavitation was present in the lower lobe. A smaller area of reddish fresh infarction was also present in this lobe and the adjacent arteries contained emboli. In the left upper lobe were two firm greyish nodules of apparent tumor tissue which measured approximately one centimeter in diameter each. The right lung was air containing in the uper lobes, firm throughout the lower lobe. Emboli were present in the arteries to the lower lobe, and the bronchi were injected and contained purulent material. On section the upper lobes were pinkish grey. In the base of the lower lobe there was a consolidation due to large firm nodules of greyish-yellow tumor tissue, the largest measuring about 5 cm. in diameter. There were numerous other smaller nodules of similar tissue, and greyish streaking along the bronchi suggestive of lymphatic involvement. The bronchial mucosa was smooth and intact and showed no evidence of tumorous involvement.

The remainder of the viscera were within normal limits with the exception of the gall bladder which contained one large stone and had a thickened scarred wall. The common duct was dilated to a diameter of about 1 cm. and was patent throughout. In the left iliac vein was a laminated greyish red smooth thrombus which extended from the femoral ring to the origin of the inferior vena cava. Lymph nodes were negative throughout, those of the bronchi and trachea appearing black and soft without gross evidence of tumor. The upper tracheal mucosa was injected and covered with some purulent exudate without gross evidence of tumor.

The microscopic examination of the right lung revealed a growth of tumor in the lower lobe which completely replaced the normal lung parenchyma. The tumor cells appeared to be of connective tissue origin, some resembling adult fibroblasts, while others were younger, more oval, and with processes (Figure 2).

The clinical findings and results of this patient have been assembled with those of the 34 previously reported cases. The following is a composite picture of the findings in 35 cases of sarcoma of the lung.

Age

0-10 years — 1	40-50 years — 6
10-20 " — 7	50-60 " — 8
20-30 " — 5	60-70 " — 4
30-40 " — 4	

Sex

Male: — 19 (54 per cent)
Female: — 16 (46 per cent)

The small number of cases makes this sex difference somewhat questionable from a statistical viewpoint.

Chief Complaint
(Most histories listed several "chief complaints")

Cough — 17
Chest Pain — 12
Dyspnea — 8

Weight Loss — 6

Weakness — 3

Fever — 4

Shoulder Pain — 3

Wheezing, precordial pain, malaise, anorexia, stupor spells, swollen extremities, none, each 2.

Arthralgia, swollen face and chest, paralysis left arm, fatigue, and palpitation, each 1.

Symptoms

Cough — 26 (74 per cent)
Weight Loss — 17 (49 per cent)
Hemoptysis — 15 (43 per cent)
Pain — 15 (43 per cent)
Fever — 15 (43 per cent)
Sputum — 12 (34 per cent)
Fatigue — 9 (26 per cent)
Effusion — 10 (35 per cent)
Dyspnea — 9 (26 per cent)
Night Sweats — 7 (20 per cent)
Chills — 2 (6 per cent)
No Symptoms — 2 (6 per cent)

In only two of the sarcoma patients were there no symptoms, the lesion having been found on routine roentgenographic study. One of these, a lymphosarcoma, replaced the entire left upper lobe, the only case in the series which corresponds with the so-called classic picture of sarcoma as a large silent tumor. The other silent mass, also a lymphosarcoma, was an isolated lesion in the right lower lobe and measured 8 cm.

Laboratory Studies

Leukocytes — (in 20 patients)
Under 10,000 — 12
10,000-15,000 — 3
15,000-20,000 — 1
Over 20,000 — 4

Erythrocytes—Hemoglobin — (in 19 patients)
Decreased — 16 (Below 4 million — 4)
Normal — 3

Sedimentation Rate — (in 4 patients)
Normal — 1
26 mm/hour — 1
95 mm/hour — 1
38 mm/hour — 1

Duration of Life After Diagnosis

(In patients who died of sarcoma)

0 Months	— 7	7 Months	— 1
1 "	— 3	11 "	— 1
2 "	— 2	12 "	— 1
4 "	— 3	13 "	— 1
5 "	— 1	18 "	— 1

Duration of Life Following Onset of Symptoms

(In patients who died of sarcoma)

1 Months	— 1	18 Months	— 1
2 "	— 3	20 "	— 1
3 "	— 1	22 "	— 1
4 "	— 1	24 "	— 1
6 "	— 1	25 "	— 1
8 "	— 1	30 "	— 1
10 "	— 2	36 "	— 1
14 "	— 1	48 "	— 1
15 "	— 1	59 "	— 1

Surgical Treatment

Procedure	Number	Living	Follow-up without evidence of recurrence
Lobectomy (one or more lobes)	5	2	14 mos., 6 mos.
		1	2 years (with recurrence)
Pneumonectomy	6	4	7½ mos., 12 mos., 18 mos., 36 mos.
Thoracotomy (with tumor removal)	4	4	19 mos., 15 mos., 7 mos., ? mos.
Thoracotomy (without tumor removal)	1	0	
Craniotomy	1	0	
"Coughed Tumor"	1	1	4 years
Died at Surgery	2	0	
Bronchoscopy with fulguration	2	2	12 mos., and ? in 1 who also had roentgen therapy

Of the total 35 cases, 17 (48.5 per cent) were amenable to surgical procedures of one sort or another. It is to be noted that in four cases the tumor could be removed at thoracotomy without sacrificing lung tissue. It is also of interest that in two instances fulguration at bronchoscopy was at least temporarily adequate, and in a third, the patient herself coughed up the tumor with no further evidence of the sarcoma four years later. Follow-up for various periods showed 59 per cent of the post-operative patients were still alive.

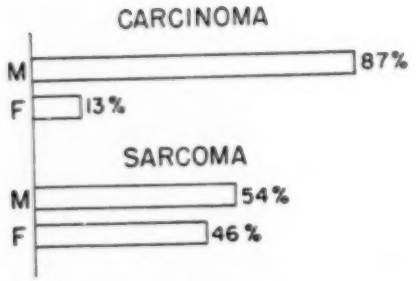


FIGURE 3

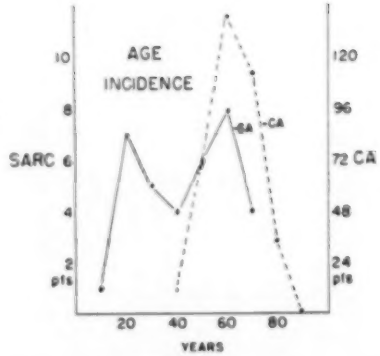


FIGURE 4

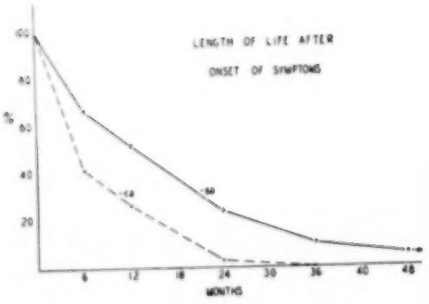


FIGURE 5

Figure 3: A Comparison of the Sex Ratios in Carcinoma of the Lung and Sarcoma of the Lung. It is apparent from Figure 3 that both types of pulmonary tumor are more common in males though the preponderance is not so great in the sarcoma patients.—*Figure 4: The Comparative Age Incidence of Primary Sarcoma and Carcinoma of the Lung.* It is well-known that carcinoma of the lung is more frequent in the later decades of life. It is also true, that cases have been known to occur at any age, including childhood. Thus, while there is a difference in the age incidence curves of the two types of tumor (Figure 4) there is considerable overlap. — *Figure 5: A Comparison of the Total Known Length of Symptoms in 22 Patients Who Died of Sarcoma with Those of 33 Cases of "Untreated" Bronchogenic Carcinoma.*[15] Figure 5 demonstrates the relatively greater longevity for patients with primary sarcoma of the lung than for those of primary carcinoma of the lung. The comparison is made with a series of untreated patients with carcinoma of the lung since the majority of the sarcoma patients who died of their disease were also untreated. The one case of sarcoma who was still living at 48 months died 59 months after onset of symptoms.

PATHOLOGY

Types of Sarcoma

Spindle cell — 15
Fibrosarcoma — 6
Lymphosarcoma — 5
Osteoid Chondrosarcoma — 1
Mixed cell sarcoma — 1
Reticulum cell sarcoma — 1
"Round cell" sarcoma — 1
Leiomyosarcoma — 1
Chondrosarcoma — 1
Plexiform sarcoma — 1
Myosarcoma — 1
Sarcoma — 1

Post-mortem examinations in which metastases were found — 10
Post-mortem examinations in which no metastases were found — 8

Location of Metastases

Lung — 8 (questionable in 1)
Local nodes — 2
Kidney — 2
Spleen — 2
Liver — 2
Brain, diaphragm, heart, each 1
Spine — 1 (questionable)

Roentgen Appearance: (see appendix)

While the traditional concept of a massive silent tumor was true in a few cases it was by no means universally so. There was no uniformity in the roentgen appearance of the pulmonary sarcomas in this series, and there was nothing to distinguish them from other types of lung tumors. In one case the sarcoma contained calcium, while several others had degenerated into necrotic abscesses. Our own patient demonstrated pleural effusion as the major roentgen finding.

Discussion

No attempt has been made to analyze the clinical picture for each of the various types of sarcoma in this series. It is felt that, while this may eventually be helpful, a much larger number of cases must be observed and reported than are now available. It is the opinion of the authors that many more of these tumors are seen than are reported. When sufficient material can be accumulated by published reports, personal communication, or tumor registration, more complete portraits of pulmonary sarcoma and its many varieties will be drawn.

There is a hint that each variety of sarcoma may have its clinical counterpart, each unique. Stout and Himadi[12] suggest that "the most

distinctive and by far the most common of the rare pulmonary tumors of the pleura is a solitary circumscribed fibrous growth which either projects outward into the pleural cavity or else extends from the pleura into the lung or chest wall. When projecting they are differentiated and benign. When buried they are anaplastic and malignant. They are composed of spindle-shaped cells and connective tissue fibers in a unique arrangement which differ from all other fibrous tumors elsewhere." His findings suggest that these mesotheliomas may indeed be a significant sub-group of the pulmonary sarcomata and as such bear special consideration and emphasis. But, again, evaluation and development along those lines will require larger numbers of such cases than are available at present.

We have not included the reported cases of carcinosarcoma. True carcinosarcomas are single lesions with both carcinomatous and sarcomatous components, found in the esophagus, uterus, larynx, bronchus, and lung. Their metastases may show a microscopic picture of carcinoma only, sarcoma only, or both. Bergmann, Ackermann, and Kemler[13] have reported in detail two carcinosarcomas of the lung which they found in a group of 258 surgically treated bronchopulmonary tumors at Barnes Hospital. In addition they discussed the features of eight previously reported tumors of this sort. They also found four so-called "collision" tumors which are the result of the chance intermingling of a carcinoma and sarcoma arising fortuitously close to one another and presenting a microscopic picture similar to carcinosarcoma. We omitted these "collision" tumors from our study.

Probably the most significant consideration of sarcoma of the lung as a group is whether or not any distinguishing diagnostic characteristics could be found. To assay this we have chosen to compare the findings in our small group with a larger and representative collection of 370 pulmonary carcinomas, reported by Moore.[14] His cases represent the experiences at Presbyterian Hospital in New York City for the years 1940 through 1949.

	Carcinoma (per cent)	Sarcoma (per cent)
Cough	78	74
Hemoptysis	51	43
Weight Loss	49	49
Chest Pain	49	43
Fever		43
Pneumonitis	30	
Weakness	20	26
Dyspnea	17	26
Wheeze	16	7

A considerable similarity in frequency of the more common symptoms is found in the two types of tumor.

Roentgen Appearance:

There are no general diagnostic differences. The features of both are found to be extremely variable, depending upon the location and size of the tumor in question. In both series are cases in which the tumor was so small that no shadow could be seen on the roentgenogram. Pleural effusions, hilar masses, silent peripheral masses, and bronchial obstruction occur in both.

Conclusion

While it is true that the ratio of females is higher, and incidence of tumor in ages below 40 is greater in primary sarcoma than in primary carcinoma of the lung, the differences are hardly diagnostic. The relative similarity in the clinical picture and roentgenographic shadows leave very little to differentiate the two types of tumor. Statistical frequency however, greatly favors carcinoma in any given case since primary sarcoma of the lung is so very rare. Surgical biopsy affords the only sure differential diagnosis.

The duration of life appears to be longer, though not universally so, in primary sarcoma than in primary carcinoma of the lung. Surgical resectability would also seem to favor the sarcoma patients on the basis of this study. In our series 48.5 per cent were resectable as compared with 24 per cent in the Presbyterian group of carcinomas reported by Moore.

SUMMARY

1) The clinical characteristics and pathology findings in primary sarcoma of the lung are evaluated on the basis of 35 cases, 34 of which have been reported in the literature and to which we have added another case.

2) Primary sarcoma of the lung is a rare tumor, found only slightly more frequently in males than in females. It occurs in persons under 40 years of age as often as it does in those over 40.

3) The clinical picture and roentgen manifestations of this type tumor can be quite similar to bronchogenic carcinoma. No distinguishing characteristics to aid in the differential diagnosis are found.

4) Surgical resectability of pulmonary sarcomas may be higher than for carcinomas of the lung.

RESUMEN

1) Las características clínicas y los hallazgos patológicos en el sarcoma primario del pulmón se estiman sobre la base de 35 casos, de los que 34 se han referido en la literatura y los cuales se agrega otro caso.

2) El sarcoma primario del pulmón es un tumor raro, encontrado sólo ligeramente más frecuentemente en los hombres que en las mujeres. Se presenta en personas menores de 40 años tan frecuentemente como más allá de esa edad.

3) Las manifestaciones clínicas y los hallazgos a los rayos X de este tipo de tumor, pueden ser muy similares a los del carcinoma bronquigénico. No se encuentran características que ayuden al diagnóstico diferencial.

4) La posibilidad de resecar los sarcomas pulmonares, puede ser mayor que la de los carcinomas.

RESUME

1) En étudiant 35 cas de sarcomes primitifs du poumon, dont 34 avaient déjà été publiés dans la littérature médicale, et auxquels les auteurs ont ajouté un cas nouveau, ils en décrivent les caractères cliniques et les constatations anatomo-pathologiques.

2) Le sarcome primitif du poumon est une tumeur rare. Il apparait aussi bien chez les personnes âgées de moins que de plus de 40 ans.

3) L'aspect clinique et les manifestations radiologiques de ce type de tumeur peut être tout à fait comparable à ce que l'on voit dans l'épithélioma bronchique. Les auteurs n'ont pas pu trouver de caractères distinctifs qui puissent permettre le diagnostic différentiel.

4) Il est possible que la résection chirurgicale du sarcome pulmonaire puisse être plus fréquemment praticable que pour le cancer du poumon.

REFERENCES

1 Hertz—Quoted in Adler, J.: "Primary Malignant Growths of the Lungs and Bronchi," *Longmans, Green and Co.*, New York, pp. 42, 1912.
2 Melville—Quoted in Graham, E. A., Singer, J. J. and Ballon, H. C.: "Surgical Diseases of the Chest," *Lea and Feibiger*, Philadelphia, pp. 846, 1935.
3 Mallory, T. B.: Cabot Case No. 22441, *N. E. J. Med.*, 215:837, 1936.
4 Ellis, R. C.: "Primary Sarcoma of the Lung with Brain Metastases," *J. Kansas Med. Soc.*, 40:243, 1939.
5 Rolleston, N. D. and Trevor, R. S.: "A Case of Primary Sarcoma of the Lung Simulating Empyema," *The Brit. Med. J.*, 1:361, 1903.
6 Johns, E. P. and Sharpe, W. C.: "Primary Pulmonary Sarcoma," *Am. J. Cancer*, 23:45, 1935.
7 Wessler, H. and Saches, L.: "Clinical Roentgenology of Diseases of the Chest," *The Southworth Co.*, Troy, New York, pp. 295, 1923.
8 Davidson, M.: "A Practical Manual of Diseases of the Chest," 2nd Ed., *Oxford Medical Publication*, pp. 489, 1941.
9 Janssen—Quoted in Adler, J.: Ibid, pp. 76.
10 Ewing, J.: "Neoplastic Diseases," 4th Ed., *W. B. Saunders Co.*, Philadelphia, pp. 883, 1949.
11 Boyd, W.: "A Text-Book of Pathology," *Lea and Feibiger*, Philadelphia, pp. 471, 1947.
12 Stout, A. P. and Himadi, G. M.: "Solitary (localized) Mesothelioma of the Pleura," *Ann. Surg.*, 133:50, 1951.
13 Bergmann, M., Ackermann, L. V. and Kemler, R. L.: "Carcino-sarcoma of the Lung," *Cancer*, 4:919, 1951.
14 Moore, R. L.: "Primary Carcinoma of the Lung," *Cancer*, 4:663, 1951.
15 Tanner, G. R. and Gordon, H.: "'Untreated' Bronchogenic Carcinoma: A Report of Thirty-Five Cases," *Am. J. Path.*, 28:953, 1952.
16 Stevens, A. A.: "Malignant Disease of the Lung with Special Reference to Sarcoma," *Am. J. Med. Sci.*, 144:193, 1912.
17 Taylor, H. L. and Caine, C. E.: "Sarcoma of the Lung," *Minn. Med.*, 1:141, 1918.
18 Pritchard, J. J.: "An Unusual Case of Pulmonary Neoplasm," *Am. J. Roent.*, 8: 555, 1921.
19 Edwards, A. T.: "Intrathoracic New Growths: An Account of Seven Operable Cases," *Brit. J. Surg.*, 14:607, 1927.
20 Pilot, I.: "Mesenchymous Tumors of Lung and Pleura," *Radiol.*, 14:391, 1930.
21 Ball, H. A.: "Primary Pulmonary Sarcoma," *Am. J. Cancer* (Supp.), 15:2319, 1931.
22 Rosenblum, P. and Gasul, B.: "A Case of a Primary Sarcoma of the Lung in an Infant Twenty-Nine Months of Age," *Arch. Ped.*, 48:63, 1931.
23 Greenspan, E. B.: "Primary Osteoid Chondrosarcoma of the Lung: Report of a Case," *Am. J. Cancer*, 18:603, 1933.
24 Baum, O. S., Richards, J. H. and Ryan, M. D.: "A Case of Atalectasis of the Right Lower and Middle Lobes with Bronchoscopy Demonstrating Spindle Cell Sarcoma of the Right Main Bronchus," *Ann. Int. Med.*, 12:699, 1938.

25 "Massachusetts General Hospital Case No. 24202," *New Eng. J. Med.*, 218:843, 1938.
26 "Massachusetts General Hospital Case No. 24472," *New Eng. J. Med.*, 219:854, 1938.
27 Steward, W. D.: "Sarcoma of the Lung," *Am. Rev. Tuberc.*, 40:224, 1939.
28 "Massachusetts General Hospital Case No. 27471," *New Eng. J. Med.*, 225:833, 1941.
29 Pollak, B. S., Cohen, S., Borrone, G. M. and Gnassi, A. M.: "Primary Sarcoma of the Bronchus," *Am. J. Roentgenol.*, 41:909, 1941.
30 "Massachusetts General Hospital Case No. 31271," *New Eng. J. Med.*, 233:18, 1945.
31 Randall, W. S. and Blades, B.: "Primary Bronchogenic Leiomyosarcoma," *Arch. Path.*, 42:543, 1946.
32 Churchill, E. D.: "Malignant Lymphoma of the Lung and Pulmonary Coccidiidomycosis," *Surg. Clin. N. Am.*, 27:1113, 1947.
33 Spatt, S. D. and Grayzel, D. M.: "Primary Lymphosarcoma of the Lung: A Case Report and Review of the Literature," *Ann. Int. Med.*, 27:632, 1947.
34 Maier, H. C.: "Primary Lymphosarcoma of the Lung," *J. Thor. Surg.*, 17:841, 1948.
35 Lowell, L. M. and Tuhy, J. E.: "Primary Chondro-sarcoma of the Lung," *J. Thor. Surg.*, 18:476, 1949.
36 Carswell, J. and Kraeft, N. H.: "Fibro-sarcoma of the Bronchus," *J. Thor. Surg.*, 19:117, 1950.
37 Curry, J. J. and Fuchs, J. E.: "Expectoration of a Fibrosarcoma," *J. Thor. Surg.*, 19:135, 1950.
38 Gray, H. K. and Whitesell, F. B.: "Primary Fibrosarcoma of the Lung," *Surg. Clin. of N. Am.*, 30:1185, 1950.
39 Beck, W. C. and Reganis, S. C.: "Primary Lymphoma of the Lung," *J. Thor. Surg.*, 22:323, 1951.
40 Behrend, A. and Kravitz, C. H.: "Sarcoma Arising in a Bronchogenic Cyst," *Surg.*, 29:142, 1951.
41 Mishkin, J. A.: "Primary Myosarcoma of the Lung," *N. Y. State J. of Med.*, 51: 1746, 1951.
42 Weissman, I. and Christie, J. M.: "Primary Lymphosarcoma of the Lung," *A. M. A. Arch. Surg.*, 62:129, 1951.

APPENDIX

Author Year	Sex Age	Roentgen Appearance	Microscopic Diagnosis
Stevens[16] 1912	M 24		Spindle Cell Sarcoma
Taylor and Caine[17] 1918	F 11	Right thorax is opaque below the 2nd rib. Heart is displaced to the extreme left.	Round Cell Sarcoma
Pritchard[18] 1912	F 23	A small distinct spheroid shadow is present in the upper part of the right lung root, 3.5 cm. in width. Sixteen months later: mass occupies entire right thorax except apex and costo-phrenic angle.	Spindle Cell Sarcoma
Edwards[19] 1927	M 60	A large, regular, rounded shadow of moderate density is seen above the diaphragm somewhat posteriorly.	Plexiform Sarcoma
Pilot[20] 1930	F 60	Large, homogeneous, dense mass, 15 cm. in diameter; sharply circumscribed in lower portion of the left lung field.	Spindle Cell Fibrosarcoma

APPENDIX (Continued)

Author Year	Sex Age	Roentgen Appearance	Microscopic Diagnosis
Ball[21] 1931	M 57	Large circumscribed density of homogenous opacity in left base, upper border not unlike diaphragm at level 7th rib posteriorly.	Spindle Cell Sarcoma
Rosenblum and Gasul[22] 1931	F 29 mo.	Superior Mediastinum, trachea and heart displaced to the left: obscurity throughout right lung; small pneumothorax in right costo-phrenic angle.	Sarcoma
Greenspan[23] 1933	F 35	Infiltration of the mesial and upper portion of the left lung. An enlarged lymph node is present in the left hilus.	Osteoid Chondrosarcoma
Johns and Sharpe[6] 1935	M 18	Moderately dense, homogenous, discrete mass 2.5 inches in diameter on the inner half of the right 1st and 2nd interspaces.	Spindle Cell Sarcoma
Cabot,[3] Case No. 22441 1936	F 47	Diaphragm high on the right with obliteration of the costophrenic angles by overlying soft tissues. A second round nodule with discrete borders seen left of the heart.	Fibrosarcoma
Baum, Richards and Ryon[24] 1938	F 29	Right lower lung field completely obscured by a density having the same appearance of elevated diaphragm plus collapsed lower and middle lobes.	Spindle Cell Sarcoma
Cabot,[25] Case No. 24202 1938	F 13	Mass 1 x 1.5 cm. protrudes into right main stem bronchus area. Right upper lobe collapsed. Right middle and lower lobes partially collapsed.	Spindle Cell Sarcoma
Cabot,[26] Case No. 24422 1938	M 63	Large, sharply defined, lobulated tumor, extending from left 5th to 9th rib posteriorly. Left costophrenic angle obliterated by fluid.	Spindle Cell Fibrosarcoma
Ellis[4] 1939	M 51		Spindle Cell Sarcoma
Steward[27] 1939	F 12	Dense shadow with some calcification occupies entire left upper; lower edge discrete. Peribronchial infiltration in remainder of the left lung.	Mixed Cell Sarcoma
Cabot,[28] Case No. 27471 1941	M 30	Small and large rounded densities in both lung fields. Large amount of fluid in the right pleural cavity.	Reticulum Cell Sarcoma
Pollak et al[29] 1941	M 19	Almost complete obliteration of the pulmonary markings on the left with marked retraction of the heart and trachea to the same side.	Spindle Cell Sarcoma

APPENDIX (Continued)

Author Year	Sex Age	Roentgen Appearance	Microscopic Diagnosis
Cabot,[30] Case No. 31271 1945	M 65	Fairly homogeneous increased density 10 x 9 x 9 cm. in posterior portion right lower lobe. An additional 3 x 2 cm. shadow overlies the right third rib on the right.	Large Tumor: Fibrosarcoma. Small Tumor: Lipoma
Randall and Blades[31] 1946	M 34	Density in right hilar region with a shift of the heart and mediastinum to the right.	Leiomyosarcoma
Churchill[32] 1947	F 45	Homogeneous density occupying the upper part of the right lung field down to the sixth rib posteriorly.	Lymphoblastoma
Spatt and Grayzel[33] 1947	F 34	Opacity in the lower right lung field peripherally with suggestion of necrotization. Two other nodular opacities seen just below and anterior to the infiltrated area.	Lymphosarcoma
Maier[34] 1948	M 50	Area of left upper lobe uniformly dense. Heart and mediastinum displaced to the left, diaphragm elevated on that side and rib spaces narrowed.	Lymphosarcoma
Lowell and Tuhy[35] 1949	F 41	Small density adjacent to the mediastinum on the left at level of 6th posterior interspace. *Twenty months later:* mass extends from 6th to 9th rib posteriorly; 20 per cent pneumothorax.	Chondrosarcoma
Carswell and Kraeft[36] 1950	M 29	Atalectasis of the lower lobe.	Spindle Cell Fibrosarcoma
Curry and Fuchs[37] 1950	F 13	Normal chest.	Fibrosarcoma
Gray and Whitesell[38] 1950	M 48	An irregular mass about 12 cm. in diameter is noted behind the right heart shadow at the left base.	Fibrosarcoma
Gray and Whitesell[38] 1950	M 58	A sharply defined rounded mass of soft tissue 9 x 6 cm. is seen in the lower portion of the right mid-thorax in the region of the inferior interlobar fissure.	Fibrosarcoma
Beck and Reganis[39] 1951	F F	A discrete, smoothly rounded shadow about 6 cm. in diameter is seen in the right lower lobe near the costophrenic angle.	Lymphosarcoma

APPENDIX (Continued)

Author Year	Sex Age	Roentgen Appearance	Microscopic Diagnosis
Behrend and Kravitz[40] 1951	M 25	Homogeneous density obscures the lower half of the right hemithorax with a horizontal "fluid" level. Immediately above this level are sharply defined nodular opacities measuring up to 4 cm. in diameter.	Fibrosarcoma
Mishkin[41] 1951	F 65	Tumor mass fills almost half entire left chest.	Myosarcoma
Stout and Himadi[12] Case No. 5 1951	M 12	A large, well-defined area of increased density is seen in the region of the long interlobar fissure in the right hemithorax.	Spindle Cell Sarcoma
Stout and Himadi[12] Case No. 6 1951	M 41	Large spherical mass, 7.5 cm. in diameter seen in the right hemithorax posteriorly.	Spindle Cell Sarcoma
Stout and Himadi[12] 1951	M 57	Rounded shadow of increased density about 3 cm. in diameter in the right lower lobe adjacent to the right border of the heart.	Spindle Cell Sarcoma
Weissman and Christie[42] 1951	M 52	Poorly circumscribed mass occupies the middle one-third of the left lung field, extending out to the periphery.	Lymphosarcoma
Noehren and McKee 1953	F 61	Opacity lower half right lung field with evidence of associated fluid.	Spindle Cell Sarcoma

Intraabdominal Complications and Sequellae of Pneumoperitoneum

R. T. FOX, M.D., F.C.C.P.,* J. R. THOMPSON, M.D., F.C.C.P.,**
O. L. BETTAG, M.D., F.C.C.P.,† E. S. GILBERT, M.D.††
and W. M. LEES, M.D., F.C.C.P.†††
Chicago, Illinois

In the past few years pneumoperitoneum has been used extensively as a therapeutic measure in patients with pulmonary tuberculosis. In our experience with this procedure at the Municipal Tuberculosis Sanitarium of Chicago, a definite clinical and pathological pattern of local reaction to intraperitoneal air has been recognized, and it is our purpose to describe this phenomenon here.

Several reports in the literature concern animal experiments with pneumoperitoneum and none of these describes any significant local pathologic changes attributed to the presence of air in the peritoneal space.[1] Trimble, Eaton and Moore,[2] in 1939, reported necropsy findings in 20 patients who had received pneumoperitoneum for varying lengths of time prior to death. Less than half showed any intraperitoneal change, and in those that did, tuberculous enterocolitis or its sequellae were thought responsible. This, of course, was in the pre-streptomycin era. In a later report Trimble et al.[3] described the intraabdominal complications encountered in their series of patients. Mitchell, et al.[4] report similar low incidence of abdominal complications.

Several authors[5-8] have discussed an apparent increase in incidence of appendicitis in patients with pneumoperitoneum, and have remarked on the poor defense reaction exhibited by these patients. Monte and Bradford,[9] Rogers and Garrett[10] and others have postulated an irritant effect of intraperitoneal air as a factor in the closure of the processus vaginalis in inguinal hernias during pneumoperitoneum therapy. Banyai[14] noted no tendency toward formation of intraabdominal adhesion as noted on resumption of pneumoperitoneum after temporary discontinuation. Corrigan[15] on the other hand reported that two out of five such cases had extensive adhesions preventing adequate reinstitution of the pneumoperitoneum.

There are many reports in the literature describing accidents incurred as a direct result of the air instillation. These include air embolism, spontaneous pneumothorax, inflation of hernial sacs, perforation of hollow or

*Assistant Chief of Surgical Service, Municipal Tuberculosis Sanitarium; Clinical Assistant in Surgery, Northwestern University Medical School.

**Chief of Laboratory Division, Municipal Tuberculosis Sanitarium; Assistant Professor of Pathology, University of Illinois Medical School.

†Chief, Department of Welfare, State of Illinois, formerly Medical Director, Municipal Tuberculosis Sanitarium.

††Assistant Chief of Medical Service, Municipal Tuberculosis Sanitarium.

†††Chief of Surgical Service, Municipal Tuberculosis Sanitarium; Assistant Professor of Surgery, Stritch School of Medicine, Loyola University.

solid abdominal viscera, etc.[11-13,16-22] Our experience with such accidents has been similar, and we shall not consider these in this report.

At the Municipal Tuberculosis Sanitarium, pneumoperitoneum has been used extensively for several years. In the years 1948 through 1952 more than 1,500 patients received pneumoperitoneum for varying lengths of time as part of their therapeutic regimen. Most of them were treated with one or more of the common anti-tuberculous drugs, dihydrostreptomycin, PAS and INH prior to or during the period in which the pneumoperitoneum was initiated. Some had temporary phrenic nerve interruption as an adjunct to the pneumoperitoneum. The specific indications and the long range therapeutic results of pneumoperitoneum will not be discussed here, but in general the patients were those with far advanced bilateral pulmonary tuberculosis. Pneumoperitoneum is ordinarily not used in persons who have any significant gastrointestinal complaints even in the absence of any demonstrable pathology. This policy was formulated when our early experience showed us that these complaints were frequently exaggerated after the induction of pneumoperitoneum, resulting in the patient's refusal to continue this treatment. Since the advent of the various antibiotics, the incidence of gastrointestinal tuberculosis has been greatly reduced. At routine necropsy in this institution, evidence of tuberculous enterocolitis has been demonstrated in only 20 per cent of patients in the past two years, as compared to 90 per cent prior to the streptomycin era.

In many of the 1,500 patients mentioned above, the pneumoperitoneum has been discontinued. Most of these were abandoned when some form of surgical collapse or excision could be substituted. Some were given up when it became obvious that the diaphragmatic elevation obtained, if any, was therapeutically ineffective. A majority showed at one time or another evidence of small amounts of intraperitoneal fluid as seen on routine fluoroscopy. Few had fluid which persisted long enough and in sufficient amount to warrant discontinuation of the air refills. Some 15 patients (1 per cent) developed intraabdominal symptoms severe enough to force abandoning pneumoperitoneum. Some of these will be described below. In only two during this four year period was there a fatality which could be directly or indirectly attributed to the use of pneumoperitoneum. These two cases will be described briefly.

Case 1: L.S., a 27 year old Japanese woman was admitted to the Sanitarium on February 11, 1949 with a diagnosis of pulmonary tuberculosis, far advanced with extensive bilateral involvement and positive sputum. Pneumoperitoneum was initiated on March 11, 1949 and maintained until June 10, 1949. The last few refills had been followed by right upper quadrant pain, nausea, vomiting and moderate febrile reaction so that finally the pneumoperitoneum was discontinued. These symptoms, though intermittent and mild in nature, persisted despite a 60-day course of daily dihydrostreptomycin. In January 1950, there was an acute exacerbation of the abdominal symptoms with high fever and loss of weight. A right subphrenic abscess was diagnosed and surgically drained on January 23, 1950. The pus contained acid fast bacilli and streptococci and other coccal organisms. Her condition improved for a few weeks, but then she became progressively worse and died on April 6, 1950. Necropsy showed that the liver was adherent to the

diaphragm by fibrinous to fibrous adhesions. The capsule of the spleen was covered by a fibrinoid coat. There was a large caseous nodule in one adrenal and the pelvic organs were bound together by dense fibrous adhesions.

Upon opening the uterus and the fallopian tubes it was found that the right tube was the seat of caseation necrosis. The gastrointestinal tract showed no ulceration but several nodular areas in the mucosa were noted.

Microscopic studies of the tissues disclosed that the fibrinous exudate between the liver and the diaphragm contained many typical epithelioid tubercles with caseation necrosis. The caseous nodule in the adrenal likewise was tuberculous in nature as was the right fallopian tube. Apparently this diffuse process throughout the peritoneal cavity had its origin from the caseous tuberculous salpingitis.

Case 2: L.F., a 45 year old white man, was admitted to the Municipal Tuberculosis Sanitarium on January 3, 1950 with a diagnosis of pulmonary tuberculosis, far advanced with positive sputum. Pneumoperitoneum was initiated on April 26, 1950 after two months of streptomycin and PAS. He was discharged, culture negative on July 7, 1951 with the classification of far advanced apparently arrested. Pneumoperitoneum was continued at one of our out-patient clinics. On December 19, 1951, one day after a pneumoperitoneum refill, he complained of abdominal pain and malaise. His condition did not seem alarming and he was observed at home until January 5, 1952 when he was readmitted to the Sanitarium as an emergency. His abdomen was markedly distended, and large amounts of air were aspirated on January 5, 1952 and January 7, 1952. A small amount of clear amber fluid was also aspirated from the abdomen at this time. He had a good appetite, and his bowels moved normally until January 20, 1952 when his condition deteriorated rapidly. The abdomen again became distended and the temperature climbed rapidly. On January 21, 1952 some 2,000 cc. of foul "pea soup" pus was aspirated from the abdomen. This fluid showed no organisms on smear, and subsequent cultures demonstrated no organisms whatsoever. The patient failed to improve despite intensive antibiotic therapy and died on January 22, 1952.

At necropsy the abdomen was markedly distended and when it was opened approximately 6,000 cc. of foul smelling purulent material was found in the peritoneal cavity. The loops of intestine were matted together, and the liver and spleen were adherent to the surrounding structures. The liver was deformed with blunting of the free margin and there was considerable thickening of the capsule over the dome which was rather typical of that change noted in other cases of pneumoperitoneum; in addition, there was purulent exudate superimposed on this fibrinoid thickening. The gastrointestinal tract was examined meticulously and no ulcerations in the mucosa could be noted at any point. The appendix was opened from the cecal ostia and the distal end of the appendix ended in and was continuous with a retro-peritoneal abscess cavity which had ruptured into the peritoneal cavity and produced this generalized peritonitis. Cultures of the abdominal fluid and sections of the various tissues failed to reveal the presence of acid-fast bacilli or tuberculous lesions.

In retrospect one can speculate that the original perforation of the appendix took place on the 19th of December and the infection remained walled-off until about one month later when it was discovered that he had generalized peritonitis. The presence of pneumoperitoneum obviously had masked the original findings and had served to prevent the normal defensive mechanisms within the abdomen from localizing the infection.

Of the 15 patients in whom severe abdominal complaints necessitated abandoning pneumoperitoneum six developed a well-defined clinical syndrome of small bowel obstruction. In each the picture was that of low-grade peritonitis with paralytic ileus rather than mechanical obstruction.

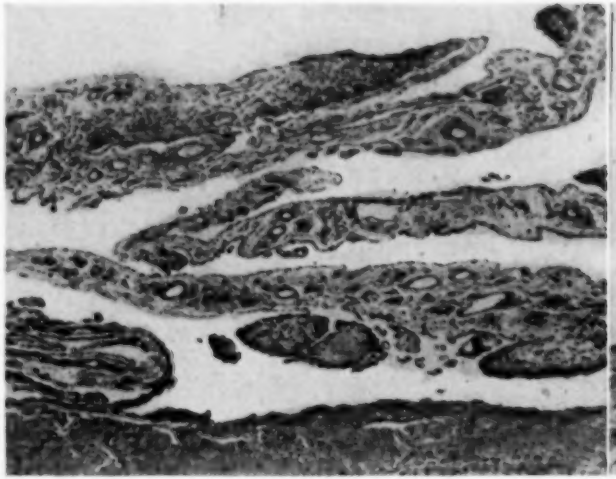


FIGURE 1

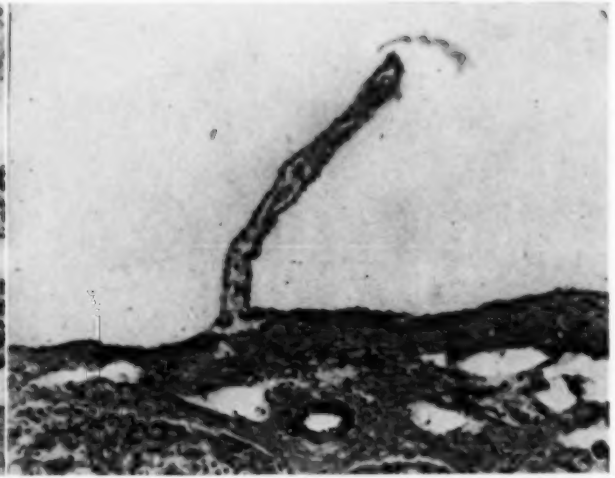


FIGURE 2

Figure 1: Photomicrograph of parietal peritoneum from a patient who had received pneumoperitoneum for 15 months. Note the piling-up of mesothelium and the vascular stroma. x50.—*Figure 2:* A thin projection of serosa with an intact mesothelial layer. x50.

All had at least a small amount of intra-peritoneal fluid, but only one had paracentesis, and the fluid obtained in this instance was sterile. All responded to conservative therapy with continuous gastric suction, antibiotics and parenteral feeding. The pneumoperitoneum in each was, of course, discontinued. Following is a representative case:

Case 3: C.A., a 40 year old white male was admitted to the Municipal Tuberculosis Sanitarium on July 1, 1949 with a diagnosis of pulmonary tuberculosis, moderately advanced with positive sputum. Pneumoperitoneum was started on July 26, 1949 because of bilateral pulmonary involvement. On December 1, 1949, three days after a refill, he began to notice slight abdominal distress. This progressed slowly until on December 8, 1949 he was markedly distended and had persistent nausea and vomiting. The temperature ran from 100 to 102 degrees F. The abdomen was tympanitic, and no bowel sounds could be heard. X-ray film showed the typical picture of a small bowel obstruction.

A Miller-Abbot tube was introduced and was seen fluoroscopically to enter the duodenum. Dihydrostreptomycin and penicillin were started and parenteral alimentation. Bowel sounds soon returned and the distension was relieved, but interruption of the suction resulted in prompt relapse on three occasions. It was not until January 6, 1950 that he was finally able to tolerate oral feedings—a total of 29 days from the initiation of decompression. He remained symptom-free thereafter and was discharged from the Sanitarium on November 21, 1950 as apparently arrested. (Old National Tuberculosis Association classification.)

Pathology:

Since early 1949 some 50 patients who received pneumoperitoneum have been studied at necropsy. In 45 (90 per cent), inflammatory changes were noted in the peritoneal surfaces—especially those covering the liver and spleen. The extent of this alteration was directly proportional to the length of time the patients received pneumoperitoneum, and, as near as we have been able to determine, no regression of this pathologic change was apparent even though pneumoperitoneum may have been abandoned some time previously.

The picture seen following a period of therapy resembles closely the condition referred to in the spleen as "sugar-coating" or "zuckerguss" which connotates a translucent pearly-gray or pale blue sheet covering the serous surface of the organ. Many times, however, the process progressed at such a rapid rate that there was a piling-up of the fibrinous and fibrous material and almost complete adhesion to surrounding structures. Oddly enough the coating in some instances seemed to be rather loosely attached to the organ and could be quite easily separated. This is comparable to the layer one finds overlying the visceral pleura following long standing pneumothorax and which, because of its loose attachment, permits successful decortication in some cases. A fibrous perihepatitis of long standing may be of such a degree as to actually deform and shift the liver from its normal shape and position. In more than one instance complete atrophy of the left lobe of the liver was noted and the free margin of the organ was displaced upward (cephalad). Just what effect this immobilization and displacement of abnormal viscera may have on function is difficult to say.

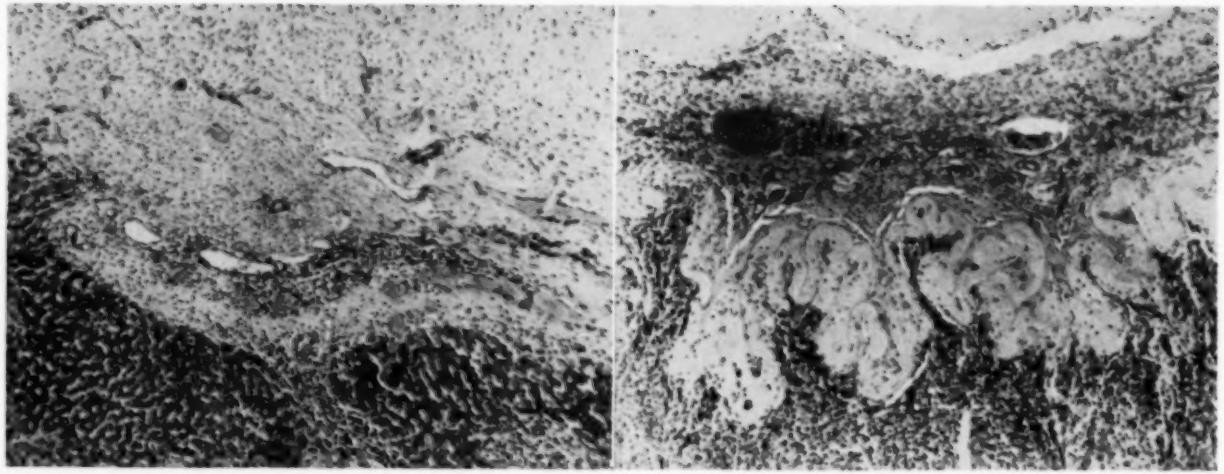


FIGURE 3

FIGURE 4

Figure 3: Photomicrograph of liver showing a marked fibrous perihepatitis with extension down into the liver parenchyma. x50.—*Figure 4:* Photomicrograph of spleen showing a thickened tortuous capsule with a fibrous membrane superimposed. Note the collections of lymphocytes in the inflammatory tissue. x50.

The peritoneum is a serous membrane which consists of two layers: a connective tissue stroma and a mesothelium. The stroma is composed of loosely arranged connective tissue bundles which interlace in a plane parallel to the surface. There are numerous elastic fibers, especially in the deeper layers, where one also finds a rich capillary network and lymphatics. The mesothelium consists of a layer of flat polygonal cells with bulging nuclei.[23] This delicate structure quickly reacts to any irritant or stimulus and one needs but to read Hertzler's[24] classic accounts of his studiees of the peritoneum to appreciate this fact. While the peritoneum has been subjected to many chemical and physical irritants, little is known about its reaction to the introduction of air. And perhaps even more important is the presence of this air under pressure. It is a well known fact that increased pressure within the peritoneal cavity reduces the rate of absorption (because of the interference with the circulation of blood), and indirectly this may have a bearing on the picture that is seen following prolonged use of pneumoperitoneum. Elevation of the diaphragm by prolonged increased intra-abdominal pressure certainly causes displacement of viscera lying close to it, especially the liver with its ligamentous attachments. In addition there may be factors related to the posture of man that have a bearing on the picture seen following pneumoperitoneum. In our laboratory air was introduced into the peritoneal cavity of guinea pigs at five to seven day intervals for a long period of time without any noticeable effect on the serous surfaces.

Microscopic studies of parietal peritoneum removed during the repair of inguinal hernias in pneumoperitoneum patients revealed, for the most part, a piling-up of the mesothelium and some increase in the vascularity of the subserous tissues. At necropsy, changes in the parietal (Figure 1)

FIGURE 5: Photomicrograph of spleen showing a thickened capsule, portions of mesothelium remaining and dense hyalinized fibrous tissue covering. x50.

were seen much less frequently and to a lesser degree than those in the visceral peritoneum. One is led to believe that the parietal peritoneum with its richer subserous layer can cope with this prolonged subjection to air pressure much better than the extremely thin serous layer covering the viscera, especially the liver and the spleen. The earliest lesion we noted was that depicted in Figure 2 where there was simply a thin outward projection of the peritoneum without any significant alteration of the mesothelium but an increase in the thickness of the subepithelial layer. One cannot say with certainty, however, that this was not an abnormal variation of a normal serous membrane as pointed out by Hertzler.

In more advanced cases the membrane seen on the peritoneal surface of the organ appeared to be dense fibrous tissue which in some instances was hyalinized. There were many large vascular spaces seen in the region of the organ capsule and the fibrous process extended down into the parenchyma of the organ (Figure 3). There is no doubt, that in some cases the capsule of the organ thickens considerably (Figure 4) before there is actually any deposition of fibrinous or fibrous material upon it. Figure 5 shows portions of the mesothelial layer still intact in spite of the layer of fibrous tissue over it.

The inflammatory process may become more marked until all semblance of normal peritoneum is eradicated and the fibrous tissue extends in a tentacular fashion over the organ (Figure 6); eventually the entire surface was involved and became adherent to the surrounding structures.

SUMMARY

Pathologic changes occurred in some 90 per cent of our cases. Speculation is made as to the pathogenesis of this process and the possible disturbance

FIGURE 6: Gross photograph of liver showing fibrous membrane covering most of its convex surface.

of abdominal visceral function. Several patients developed low grade peritonitis with a dynamic small bowel obstruction. All responded to nonsurgical management. Pneumoperitoneum has been definitely incriminated as contributing to death in two patients. The overall incidence of significant complication has been about 1 per cent.

RESUMEN

Ocurrieron cambios patológicos en aproximadamente 90 por ciento de nuestros casos. Se especula acerca de la patogenia de este proceso y el trastorno posible de la función de las vísceras abdominales. Varios enfermos presentaron peritonitis poco grave con obstrucción dinámica del intestino delgado. Todos respondieron al tratamiento no quirúrgico. El neumoperitoneo ha sido incriminado definidamente como factor contribuyente a la muerte de dos enfermos. La incidencia total de complicaciones importantes es aproximadamente de uno por ciento.

RESUME

Les auteurs ont constaté des altérations anatomiques dans environ 90% de leurs cas. Ils envisagent la pathogénie de ce processus et la possibilité d'un dérèglement de la fonction des viscères abdominaux. Plusieurs malades furent atteints d'un lent degré de péritonite avec occlusion paralytique de l'intestin grêle. On obtint pour tous de bons résultats sans faire appel au traitement chirurgical. Chez deux malades, on à pu admettre avec certitude que le pneumopéritoine avait contribué à la mort. La moyenne des complications dans l'ensemble fut de 1%.

REFERENCES

1 Overholt, R. H.: "Air in the Peritoneal Cavity," *Arch. Surg.*, 21:1283, 1930.

2 Trimble, H. G., Eaton, J. L. and Moore, G.: "Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis," *Am. Rev. Tuberc.*, 39:528, 1939.

3 Trimble, H. G., et al.: "Pneumoperitoneum in Treatment of Pulmonary Tuberculosis in 407 Consecutive Cases," *Am. Rev. Tuberc.*, 57:433, 1948.

4 Mitchell, R. S., Hiatt, J. S., McCain, P. P., Eason, H. F. and Thomas, C. D.: "Pneumoperitoneum in Treatment of Pulmonary Tuberculosis," *Am. Rev. Tuberc.*, 55:306, 1947.

5 Habeeb and Reiser: "Pneumoperitoneum with Phrenic Paralysis for Pulmonary Tuberculosis," *Am. Rev. Tuberc.*, 61:323, 1950.

6 Knoepp, L. F.: "Acute Appendicitis Occurring During Therapeutic Pneumoperitoneum," *Dis. of Chest*, 17:584, 1950.

7 Schaff, B. and Bernstein, S.: "Appendicitis During Pneumoperitoneum Treatment," *Am. Rev. Tuberc.*, 61:353, 1950.

8 Brieger, F.: "Complications of Pneumoperitoneum Therapy of Pulmonary Tuberculosis," *Beitr. Klin. Tuberk.*, 102:398, 1949.

9 Monto, R. W. and Bradford, H. A.: "Scrotal Pneumocele as Complication of Pneumoperitoneum," *Am. Rev. Tuberc.*, 47:537, 1943.

10 Rogers, W. N. and Garrett, J. V.: "Scrotal Pneumocele as Transient Complication of Pneumoperitoneum," *Brit. J. Tuberc.*, 41:70, 1947.

11 Stein, Hans F.: "Complications of Artificial Pneumoperitoneum," *Am. Rev. Tuberc.*, 64:645, 1951.

12 Hurst, A., Maier, H. M. and Dwork, R.: "Critical Study of Pneumoperitoneum and Phrenic Nerve Crush in Pulmonary Tuberculosis," *Dis. of Chest*, 13:345, 1947.

13 Cornwall, V. Catton and Patridge, W. H.: "Fatal Peritoneal Hemorrhage Complicating Pneumoperitoneum Case," *Tubercle*, 28:164, 1947.

14 Banyai, A. L.: "Intraperitoneal Pressure During Treatment with Pneumoperitoneum. Clinical Study," *Arch. Int. Med.*, 63:547, 1939.

15 Corrigan, F. T.: "Adhesion Formation After Pneumoperitoneum," *Tubercle*, 28: 25, 1947.

16 Yannitelli, S. A., Woodruff, C. E., Mueller, E. E. and Howard, W. T.: "Fatal Tension Pneumothorax Resulting from Diaphragmatic Rupture in Patient Receiving Pneumoperitoneum," *Am. Rev. Tuberc.*, 60:794, 1949.

17 Warring, F. C. Jr. and Thomas, R. M.: "Spontaneous Air Embolism Observed in Case," *Am. Rev. Tuberc.*, 42:682, 1940.

18 Bailey, W. H.: "Air Embolus in Pneumoperitoneum; Fatal Case," *Am. Rev. Tuberc.*, 57:621, 1948.

19 Burgos, R.: "Accidents and Complications in Therapy of Intestinal Tuberculosis," *Joja Tisiol.*, 6:232, 1946.

20 Meltzer, H.: "Scrotal Pneumocele Complicating Artificial Pneumoperitoneum," *Brit. J. Tuberc.*, 42:70, 1948.

21 Nagley, M. M.: "Scrotal Pneumocele and Inguinal Hernia Complicating Pneumoperitoneum Therapy," *Brit. J. Tuberc.*, 42:17, 1948.

22 Banyai, J. L. and Jurgens, G. H.: "Mediastinal Emphysema as Complication of Pneumoperitoneum," *J. Thor. Surg.*, 8:329, 1939.

23 Hertzler, A. E.: "Surgical Pathology of the Peritoneum," 1935, Chapters I, II and IV.

24 Smith, P. E.: "Bailey's Text-book of Histology," 1940, Pp. 460-461.

Pneumoperitoneum Therapy: Some Contraindications; Anatomy of Omental Bursa*

JOSEPH C. MULHERN, M.D., F.C.C.P.
Sanatorium, Mississippi

The purpose of this article is (a) to present what are considered to be some contraindications to maintenance of pneumoperitoneum, (b) review briefly the anatomy of the omental bursa and rationalize the problem of air intermittently entering the omental bursa through Winslow's foramen dependent on position of the patient.

Anatomy of the Omental Bursa. The omental bursa is a deep pouch of peritoneum communicating with the general peritoneal cavity by means of the epiploic foramen (foramen of Winslow). The omental bursa lies chiefly on the left side of the body in the upper part of the peritoneal cavity. The epiploic foramen lies to the right of the median line. The anterior wall of the bursa is formed principally by the lesser omentum. The posterior wall is formed mainly by the body and tail of the pancreas. The inferior portion is bounded by the transverse mesocolon. There is an inferior recess which descends into the greater omentum. The depth of this recess shows great individual variation and with advancing age tends to become obliterated in its lower portion.

Winslow's foramen is comprised of three ligaments: (1) Hepato-duodenal (anterior). (2) Hepato-renal (posterior). (3) Duodeno-renal (posterior). The left recess or border of the omental bursa is formed by (a) spleno-renal ligaments, (b) spleno-pancreatic ligaments. Inasmuch as the blood supply to the spleen and stomach are in relatively close relationship, enumeration of the principal vessels is indicated. They are as follows:

Arterial Supply:

Coeliac Axis, branches of which are:

A. Left Gastric
B. Hepatic
C. Spleen
    1. Pancreatic
    2. Left gastro-epiploic
    3. Short gastrics to fundus
    4. Branches of hilus of spleen.

Venous return consists principally of the *portal vein* formed by the union of the superior mesenteric and splenic veins behind the neck of the pancreas. It continues in the region of the pancreatic notch the course of the superior mesenteric and enters the hepato-duodenal ligament which forms the anterior portion of foramen of Winslow.

The blood supply of the spleen enters at the hilus and it is certainly

*From the Mississippi State Sanatorium.

CASE 3

CASE 2

CASE 1

conceivable that in undue torsion, as in Case 1, the blood supply to the spleen could well be compromised, leading either to actual necrosis or embolic threat. The short gastrics to the fundus of the stomach emanate in part from the splenic artery and could also be compromised.

It is conceivable, therefore, that air entering the omental bursa intermittently through the foramen of Winslow can account for the relatively sudden appearance and disappearance of some entities which have been named pneumatoceles. It is our opinion that Case 5 could well represent such an occurrence. It may here be mentioned that it was ascertained that the appearance of the encapsulated air was but for a short period of time and was not gastric air.

Case 1: L. S., a 67 year old male with no antecedent history which might account either by trauma or infection for the persistence of adherence of spleen to the left hemi-diaphragm. As will be noted in the illustration, the spleen is under tension and torsion; the gastro-lienal and pancreatico-lienal ligaments are in the main accountable for the lunar conformation of the spleen in this instance. It was our opinion that continuance of refills in this case would be quite hazardous.

Case 2: L. W., a 35 year old male. The hepatic capsule is under tension and there are several almost arachnoidal adhesions not too well brought out on the reproduction. Continuance of refills in this case was also considered to be hazardous and therefore abandoned.

Case 3: E. P., 28 year old female. In addition to hepatic adhesions, this illustration displays what is considered to be an accessory spleen. It will also be noted that the bowel is depressed markedly toward the pelvis accounting for a certain measure of the abdominal distress experienced by this patient coincident to refills. The pneumoperitoneum was abandoned.

Case 4: F. M., 42 year old female. Note thin-walled diaphragmatic protrusion on the right (Illustration 4C) which simulates bowel herniation into the chest cavity. (Illustration 4A, February 7, 1952; 4B, April 10, 1952; 4C, May 13, 1952). It might be noted that Case 4 was considered to be extremely hazardous to maintain because of destroyed left lung, and should there have been a rupture of the right hemi-diaphragm with a resultant pneumothorax on the right, chances of survival would have been minimal.

Case 5: W. D., 45 year old male, is considered to illustrate air in the omental bursa. This is not thought to be gastric air. (This was ascertained on fluoroscopy). Manipulation of the patient was of necessity minimal, and the tomographic procedure was not considered feasible because he was having hemoptysis due to mediastinal calcification. (He could not be moved.) While this illustration is presented with the purpose of helping to eliminate the ambiguous term pneumatocoele, the calcification seen in the mediastinum could well be considered a contraindication to pneumoperitoneum were the pulmonary haemorrhage to have increased concomitant to pneumoperitoneum.

Discussion

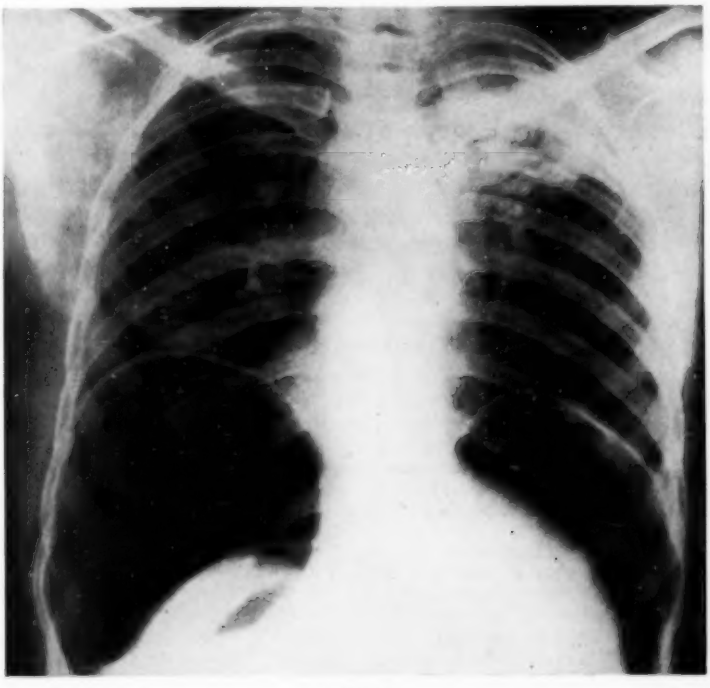
Cases 1 through 4 comprise what we considered contraindications to maintenance of pneumoperitoneum. In Case 4 particularly, the rather rapid appearance of the diaphragmatic eventration and/or bleb illustrates the necessity of maintaining close watch on all pneumoperitoneum cases, regardless of how long the individual has been receiving pneumoperitoneum.

4C 4B 4A

CASE 4

In this case, pneumoperitoneum had been present for more than 14 months before entrance to the institution and the diaphragmatic protrusion appeared and enlarged in a relatively short time. It is conceivable that if the protrusion were to have occurred while this patient was still being cared for by private physician and were it to have ruptured, results could have been disastrous.

It should perhaps be mentioned parenthetically that it is the opinion of Anderson and Winn[1] that abdominal and subdiaphragmatic adhesions were present in 71 per cent of their patients and are considered to be a compromising factor when such patients are presented with pneumoperitoneum. Hans Stein's[2] excellent review of complications of pneumoperitoneum certainly would bear re-reading occasionally by those engaged in pneumoperitoneum therapy. It is our opinion also that the pain experienced by the hyper-esthetic tuberculous peritonitis case, even though the peritonitis be resolving, speaks against too vigorous treatment. Judiciously timed, relatively small injections of air intraperitoneally, are certainly warranted as opposed to the relatively large injections which are considered by some to be necessary to effect healing of lung parenchyma. It is also worthy of comment that Banyai's[3] statement several years ago that pneumoperitoneum is a *physiological* method of treatment has been given too little heed by some operators. There are still too many patients who are



CASE 5

dyspnoeic while ambulatory and some border line *cor pulmonales* due to the rather phlegmatic attitude of some who are inclined to regard this as an innocuous procedure. Before coming into its own, pneumoperitoneum had more than enough detraction, and now it seems that it is suffering from over-enthusiasm by those of us who continually ignore physiological principles.

SUMMARY

1) Five cases have been presented which are considered to be representative of some contraindications to the continuance of pneumoperitoneum.

2) The anatomy of the omental bursa has been reviewed and an endeavor made to correlate the appearance of pneumatoceles with possible distension of the omental bursa.

3) Opinion has been expressed that pneumoperitoneum should be treated with the respect, if not the delicacy, accorded pneumothorax in previous years.

RESUMEN

1) Se presentan cinco casos que se consideran representativos de algunas contraindicaciones para la continuación del neumoperitoneo.

2) Se revisa la anatomía de la bolsa omental a fin de correlacionarla con la aparición de neumatoceles con posible distensión de ella.

3) Se expresa la opinión de que el neumoperitoneo debe ser tratado con el cuidado si no es que con la delicadeza concedida al neumotórax años atrás.

RESUME

1) L'auteur présente cinq cas qu'il considère comme reprèsentatifs de quelques contre-indications à continuer le pneumopéritoine.

2) Il rappelle l'anatomie du "tablier omental" et explique que sa dilatation possible par l'air puisse réaliser des sortes de pneumatocèles.

3) Il exprime l'opinion que le pneumopéritoine devrait être traité avec le respect, sinon la délicatesse que l'on s'imposait pour le pneumothorax dans les années antérieures.

REFERENCES

1 Anderson, N. L. and Winn, W. D.: "Pneumoperitoneum and Diaphragmatic Paralysis," *Am. Rev. Tuberc.*, 52:380, 1945.

2 Stein, Hans F.: "Complications of Artificial Pneumoperitoneum," *Am. Rev. Tuberc.*, 64:645, 1951.

3 Banyai, A. L.: "Pneumoperitoneum Treatment," The C. V. Mosby Company, St. Louis, Missouri, 1946.

4 Banyai, A. L. and Jurgens, G. H.: "Accidental Pneumothorax During Pneumoperitoneum Treatment," *Am. Rev. Tuberc.*, 42:688, 1940.

5 Banyai, A. L. and Jurgens, G. H.: "Mediastinal Emphysema as Complication of Pneumoperitoneum," *J. Thoracic Surg.*, 8:329, 1939.

6 Harrell, C. L.: "Pneumoperitoneum in the Treatment of Pulmonary and Abdominal Tuberculosis," *Dis. of Chest*, 6:273, 1940.

7 Middleton, J. W., Pickett, W. H. and Singleton, A. O. Jr.: "Torsion of the Spleen Associated with Pneumoperitoneum," *Am. Rev. Tuberc.*, 62:439, 1950.

8 Leucutia, T.: "Pneumoperitoneum and Pneumoretroperitoneum," *Am. J. Roentg. Radium Ther. and Nuclear Med.*, 68:655, 1952.

9 Elliott, J. L. and Blair, Emil: "Artificial Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis," *Dis. of Chest*, 20:520, 1951.

10 Barach, Alvin L., Beck and Eastlake: "Venous Pressure as a Guide to Pneumoperitoneum Therapy in Pulmonary Emphysema," *Dis. of Chest*, 22:130, 1952.

11 Nozzoli, Franco, Epstein and Molnar: "Right-sided Spontaneous Pneumothorax and Peritoneal Effusion Complicating Therapeutic Pneumoperitoneum," *Am. Rev. Tuberc.*, 66:90, 1952.

12 Pollak, Ann: "The Effect of Pneumoperitoneum on the Electrocardiogram," *Dis. of Chest*, 19:36, 1951.

13 Epstein, Isaac: "Spontaneous Pneumothorax Due to Diaphragmatic Defect Complicating Pneumoperitoneum Therapy," *Dis. of Chest*, 20:327, 1951.

14 Brock, Benjamin L.: "Streptomycin and Artificial Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis," *Dis. of Chest*, 16:411, 1951.

Cytology—A Means of Learning Disease Processes

SEYMOUR M. FARBER, M.D., F.C.C.P.*
San Francisco, California

The diagnosis and management of chest diseases has traditionally been approached from a clinical point of view, so far as teaching is concerned. Almost since the beginning of specialization, a large part of the medical student's knowledge of this field of medicine has been acquired by actual experience in chest service wards. On the whole, at the University of California we have concluded that this is the best teaching procedure and with this philosophy clinical emphasis has been maintained in the approach to pulmonary exfoliative cytology.

The pulmonary cytology laboratory around which this clinical work centers is a part of the complete cytologic service maintained by the University of California Cancer Research Institute. We are fortunate also in that it is conducted as an integral part of the 245-bed University Tuberculosis Division of the San Francisco Hospital. Every student spends four weeks working in and around this tuberculosis service, and a large part of his training consists of complete "work-ups" on various patients. Actual experience with cytology is focused around these clinical studies: cytologic evaluations are a routine part of this procedure. The student submits sputum specimens, evaluates the reports, and studies the smears. He is encouraged to discuss cytologic findings with laboratory personnel, and is expected to have at least a firm understanding of the criteria upon which cytological interpretation depends.

The student is encouraged to take an active part in the various studies, and procedures carried out in the laboratory. A cytology laboratory cannot exist upon only sputum specimens or bronchoscopically obtained specimens, particularly since the full potential of the technique has by no means been realized at the present time. Every case must be followed to a final clinical diagnosis, with continual re-evaluation of cytologic appearances in terms of further clinical findings. In particular, every effort is made to secure surgical or autopsy specimens for comparison with cytological materials. The significant place that this continued research plays in our present cytology set-up is indicated by the fact that the Director of the Laboratory, Dr. David A. Wood, a pathologist is also in charge of the Cancer Research Institute of the University.

The student is encouraged to participate in this continuing research, particularly as his own patients are effected. He is further encouraged to integrate cytologic findings with other clinical and pathological data for

*From the Cancer Research Institute and the Department of Medicine, University of California School of Medicine, and the San Francisco Department of Public Health, San Francisco Hospital, California.

The ninth in a series of articles prepared under the sponsorship of the Council on Undergraduate Medical Education of the American College of Chest Physicians.

himself, and to discuss his conclusions with his instructors in the laboratory. The object of this program is to teach the student not only potential usefulness, as well as the limitations, of cytology, but to give him a broad understanding of the essential principles upon which its use depends. We hope to train a generation of doctors who will use cytologic findings as familiarly and as competently as this present generation uses roentgenologic techniques. The actual cytologic diagnosis must remain a matter for highly-trained specialists, but it can only be fully effective if the widest possible understanding of the technique exists in the medical profession as a whole.

The student's acquaintance with cytology does not end with his period of study in the tuberculosis wards. In his further medical training he will spend much time among the approximately 700 non-tuberculous patients in other wards of the San Francisco Hospital. He is encouraged to make full use of the cytologic laboratory in diagnosing his new patients. In our experience, we have found that the cytologic training the student receives while assigned to the tuberculosis wards does enable him to make full and intelligent use of the laboratory during his other training.

It is our conviction, however, that a proper use of cytology will help keep the whole field of chest diseases in proper perspective. The reason for this conviction is the nature of cytologic findings. The various tests for acid-fast bacilli are very much yes-or-no matters. Cytologic appearances, on the other hand, reflect with considerable accuracy the type of pathologic lesion present in the lung, malignant or not. Much of the problem in the development of cytology, as a matter of fact, has been the necessity for the narrowing of the criteria for malignancy. In early experience with the technique a great range of non-malignant processes, especially asthma, tended to lead to false positive diagnosis simply because the cellular distortion seen was at time so extreme. Although it has so far seemed desirable to confine formal cytologic reports to the simple question of malignant or non-malignant, a trained cytologist can suggest with reasonable assurance the cellular appearances characteristic of numerous non-malignant conditions, from simple inflammation through chronic inflammatory processes such as bronchiectasis and Friedlander's pneumonia to the common fungus diseases and pulmonary adenomatosis. By providing for the close cooperation of the laboratory with the individual student working with specific cases, the great range of possible chest abnormalities is emphasized.

In the last place, we believe that this close liaison provides for a better understanding of the *process* of chest disease. Cytologic studies focus attention upon the basic unit of the body, the thing which is primarily damaged—the cell. Cytologic procedures preserve the individual cells with a minimum of distortion, very much as they would appear if they could be stained and viewed in their original place in the bronchial tree. We believe that this accurate visualization for a great range of diseases cannot but contribute to that process of disciplined imagination and application which is the essence of good diagnosis.

Knowledge Is Not Enough*

ALVIS E. GREER, M.D., F.A.C.P., F.C.C.P.
Houston, Texas

It is my privilege as President of the American College of Chest Physicians to greet you tonight and commend you for the splendid achievements of the Missouri Chapter of the College. Furthermore, I am grateful for the opportunity of being with you—my personal friends—at this dinner culminating a day of scientific discussion. I will discuss most briefly some of the indeterminate factors I consider essential to the continued growth and progress of the science of medicine to the attainment of the ever-receding goal—health and happiness for man.

I have become conscious, increasingly and progressively, throughout the years of the inadequacy of present-day methods of education to prepare our young men for the present and future problems of life. I will talk to you tonight on the subject, "Knowledge Is Not Enough". Let me interpret the word, "knowledge" as acquaintance, or clear perception of, facts, in contradistinction to wisdom which is the ability to judge soundly or deal sagaciously with facts (knowledge) in an endeavor to relate them to life and conduct. Intelligence may be defined as mental acuteness. It is pertinent to add that the posession of intelligence and knowledge alone do not constitute wisdom. We attain knowledge from thoughts of other men; wisdom dwells in heads whose minds are attentive to their own. A man may possess wisdom without knowing many things, nor even knowing them thoroughly, but possessing ability in choosing what conduces the most certainly to our true happiness and eternal glory. Tennyson has said, "Knowledge is earthly of the mind, but wisdom, heavenly of the soul".

It should be the ideal of the universities to serve up what may be termed "solid knowledge"—meaning present-day facts, combined with efforts to promote individual thinking and to stress the objective of education is to contribute to life itself—not to selfish egotism and goal, alone. It is not the business of a university to serve gobbets of prepared essays to the end the pupil will absorb facts in a parrot-like fashion. The pupil must be taught that life is enduring and permanent and that knowledge with wisdom may be gained from history, inculcating in his mind the future lies before him, stressing that present knowledge, alone, is not enough. It is in such a manner true physicians may be taught to subordinate self for the future.

When did all this confusion start? It is my humble opinion it began with the establishment of progressive education in our public schools, aided and abetted later in our colleges. This philosophy teaches there is nothing fixed or permanent, and there is nothing to be gained from the philosophic observations of the past. It attempts to make oneness in the pupil, keeping the bright on the level with the backward; de-emphasizes

*Address delivered at the Missouri Chapter Banquet, Interim Session, American College of Chest Physicians, St. Louis, November 29, 1953.

the fundamentals in order to stress sociological subjects. It teaches results are pre-eminent, the means subordinate.

Have we forgotten that man is identified by the fact that he should be trying to decipher the meaning of things—to ponder the riddles of existence? It must be instinctive in man to be concerned with these eternal questions if he is to be identified as a man. I am positive each of us has a mission in life, and that every one of us feels or has felt it. The capacity for such noble feelings is in most persons a very tender plant, easily killed, not only by hostile influences but by mere want of sustenance. In young persons it rapidly dies away if their teaching, training and professional influences are not favorable in keeping that higher capacity in action. They, thereby, lose their higher ideals and hopes, and then lose their intellectual tastes.

We are failing to some extent as teachers in hospitals, clinics and medical schools. We hurry our students through a crowded curriculum to make room for the next class. The student has hardly had time to get a good breath, much less have time to think. What a spectacle! At age six he entered grade school, age 17 started four long years of preliminary college work, was graduated in medicine at age 25, one year in a hospital, three years postgraduate training, and at age 29 he is a specialist. Hurry! Hurry! Such a marathon! Is he educated? Yes, superbly; with many facts, both isolated and connected. No lad without high ideals would embark upon such a long, long journey. Did we keep before him the proper sustenance, by our influence and individual counsel, to enable him to keep alive wonderment of the riddles of our existence and his instinctive concern of the eternal problems of life? He must be taught not only the right principles but he must be made to love them.

There is something infinitely deeper than the acquisition of knowledge as knowledge. It is just as true that we cannot depend upon the perceptions of our senses. And that thing is the search for truth which has no limit but Life itself. We are becoming bound down in our teaching and training by traditionally set formulas and the influence of dominant classes, who may stultify free thinking. Frankly, I revere tradition—that is traditional good—but all of tradition is difficult to rationalize. Criticism of tradition is not wrong; it will not cause the good to crumble. To my mind all traditional factors are good—even, perhaps if tinctured with some superstition—if they tend to produce insight and happiness into and beyond the present scientific progress of civilization; if the reverse occurs, I deplore it.

We cannot have a set formula for scientific progress. We must break the chains of oppressive thinking if we are to progress. You are thinking, perhaps, that if we break a link or two with tradition the result will be dissatisfaction with ourselves and the present. You are right in that thought. It is to be remembered one great element of humility is dissatisfaction with one's present status. It is better to be a human being dissatisfied than a pig satisfied; better to be Socrates dissatisfied than a fool satisfied. This difference of opinion is that the pig and the fool know only one side of life.

The horizon of the future is wide open for the younger men in medicine because the possibilities are in excess of the actualities. The thrill of the chase is his own. He must be taught that things not revealed to our knowledge may really in themselves be ambiguous, and that actualities float in a wide sea of possibilities.

I pray you will not gain the idea I am at loggerheads with science and scientific teaching, for such is not the case. It is my firm conviction that the man-made progress of the future rests with science and vision. And may I state, there is and will not be vision except with God. Although science professes to draw no conclusions but such as are based on fact, things that had actually happened, how can any amount of assurance that something actually happened give us any information as to whether things might or might not have happened in its place. In such a matter the wheels of chance may have turned one way or the other.

My express plea is that we must instill into our younger men a rationalistic attitude. Their minds must not be bound down and oppressed by the acquisition of facts, alone. Their minds must not be fettered by parrot-like teaching without philosophy and vision; they must be made to know the horizon lies just beyond. The necessity for practice and experience is mandatory—more clinic and hospital patients to observe. For it is only through practice and experience a theory can be tested. In such a way the physician can become a true friend of humanity with a rational attitude toward ethical, humanistic, and scientific observances.

I admit frankly, in closing these observations, that I am a humanistic optimist. Instead of visualizing man as nobly facing ultimate extinction of life and hope, I see man going indomitably on, despite recessions of error, toward an ever receding goal of increasing perfection.

The President's Message

Do you wonder what the President of the American College of Chest Physicians is thinking as his term of office is drawing to a close? I do not know what others have thought—perhaps, the same as I—but, if you will draw around closely I will tell you of my thoughts and impressions during these final days. Would that we could visit this afternoon in the quietness of my library; perhaps, then, I could talk intimately to you of my increasing awareness of the greatness of this organization, and what it means to me, and I pray, to you.

It is not for today we are striving; on the morrow, today will be the past. Perhaps, today, or this year, we may not be able to visualize the fruits of our efforts—the summation of all the work which makes this College a dynamic and living force for the betterment of Man. What we have done—the parts of the whole—we well know, but of the results—the product—we can only visualize in a shadowy way; we know little about the ultimate attainment of our goal. I find encouragement when the realization arises of my personal inadequacies and lack of tangible achievement, from a verse by Clough, as follows:

> *"And not by eastern windows only,*
> *When daylight comes, comes the light;*
> *In front, the sun climbs slow, but slowly;*
> *But westward, look, the land is bright".*

We hear occasionally the voiced plaint "I would love to be a part of the College organization, if I had the opportunity". You and I know every member has the opportunity to help "carry the ball"; the College is made up of individual members of the same status and perogatives. Every member of the College should take an active, individual part in its activities. It is equally impossible to know the workings of the College as a whole without knowing the parts in detail. The College office in Chicago will welcome you at any time you chance to be in Chicago, and acquaint you with its efforts to serve you. For men like you formulate the policies and principles of your organization for this year and the years to come. We need members with ideas. There is always a dearth of ideas; we must not consider such a lack as a disaster—it is your opportunity. Our principles may be valid although we cannot say what or how much. You must not go on day by day, plodding an appointed round without reflection, without reason, simply because you expect someone else to do your thinking and acting for you. We need in this College more men who realize there are many parts to the whole and that the whole consists of a great number of parts. The College has attained a stature making it imperative to choose its members wisely. It is not quantity alone we should seek; the quality of the membership is the paramount and true objective—men of ideas, initiative, and, yes, with dreams, if you please. Men with mental inertia have no place in this College. Let me repeat, we must have quality, not necessarily quantity, as our goal. The reason some people do not recognize an opportunity when

they meet it, is that it usually goes around wearing overalls and looking like hard work. One man who "wears his overalls" is Mr. Murray Kornfeld, and without his tremendous capacity for work, executive and organizational genius, counsel and experience, no president could fulfill his duties. Every member of this College has his ideas and wills, some good, some bad, but we must have concert in our actions and policies. It is true that where there's a will there's a way, but when there are too many wills, there's no way. We must not be disconnected in our quest for the ultimate good in life; design and purpose are necessities. The manner in which we chart our future is the only way we shall be able to introduce any order or system in it, and give it any meaning at all. The future lies in a world of shadows, our present knowledge may be ambiguous and only symbolic of the future. Whatever our present thoughts and ideas may be, we must pursue every angle to its involvement if we are to progress to our ultimate goal. This goal is not for personal greed, individually or collectively; we must not be hampered by our passions and desires—such alien distractions will divert us from our course. We must believe with all our hearts and souls in the College and its destiny, or it will resolve into mere chaos.

When I speak of a "goal" I do not presume to mean finality—the Ultimate—the Infinite—which we can only faintly visualize. We are merely workers in the vineyard, attempting to advance the progress of Life's problems, looking forward, advancing step by step, if we can, into the Unknown, hoping to add to, not detract from, the progress of humanity toward a better and fuller life. As for myself, personally, it is my fervent desire to go on with you through the years to come, working for the College, its purposes, aims, and its philosophies. We must believe in the possibilities of our dreams if we are to attain their fulfillment. I know that just as soon as I abandon my principles of choice about the good in life and the College, there would be nothing else to fall back on. And, furthermore, any member who discards his "overalls" and rests on his laurels will discover they are only poison ivy. I love the College—its principles, objectives, and all of you—and may God give us many years together in His work.

Alvis E. Greer

Obituary

HERBERT L. MANTZ, M.D.

1896 - 1953

Herbert L. Mantz

Dr. Herbert L. Mantz, who died on December 14, 1953, at his home in Kansas City, Missouri, was born at West Plains, Missouri, on June 28, 1896. He attended the grade and high school of West Plains.

His university training was started at the University of the South in the school year of 1914 to 1915. From 1915 to 1916 he attended Washington University of St. Louis, and spent the summer term at the University of Chicago. The next two years he studied at the University of Missouri.

In the First World War, Dr. Mantz was a member of the U. S. Army Reserve, and in 1918 was a private in the Student's Army Training Corp of the Jefferson Medical College. He graduated from that college in 1920. His internship and postgraduate work was received at the Kansas City General Hospital and the Kansas City Tuberculosis Hospital. Dr. Mantz had been in private practice in Kansas City since 1921, and in addition was controller of tuberculosis for Kansas City until the time of his death. During the Second World War, he was a consultant in chest disease for the Selective Service.

Dr. Mantz was a member of the Staff of St. Mary's Hospital, the Kansas City General Hospital, and the Kansas City Tuberculosis Hospital. He was Chief National Consultant in the tuberculosis program of the Veterans Administration, and a consultant for the tuberculosis section of the United States Public Health Service. He was also Chief Medical Consultant for the Missouri Bureau of Vocational Rehabilitation.

Dr. Mantz' organizational affiliations included the Jackson County Medical Society for which he was once Editor of the Weekly Bulletin, and the Kansas City Southwest Clinical Society for which, at the time of his death, he was on the Executive Board. He was a past president of the National Tuberculosis Association, of the Mississippi Valley Trudeau Society, and of the Missouri Tuberculosis Association. At the time of his death he served on the National and Regional Committees on Postgraduate Medical Education for the American Trudeau Society.

He also was a member of the American Association of Industrial Physicians and Surgeons, and of the American College of Chest Physicians, serving as a Regent for that organization. He was a past president of the Missouri Chapter of the American College of Chest Physicians.

Dr. Mantz married Mary Eager Reese on June 18, 1921. Their four children are: Ben Reese Mantz of Beverly Hills, California, Mrs. Robert Stooker, Tulsa, Oklahoma, Mrs. Richard Griffith, Kansas City, Missouri, and William Walter Mantz, who is a freshman at the University of Colorado in Boulder, Colorado.

In 1951, Dr. Mantz was presented a gold key by the Jackson County Medical Society for his outstanding contribution in the field of tuberculosis.

In addition to his many professional activities, Dr. Mantz had many non-medical

interests. He was a member of the Kansas City University Club. He was, for many years, a deacon of the First Baptist Church and on the Board of Trustees, active in the Fund Raising Campaign for the Baptist Memorial Hospital.

Throughout his entire medical life, he wedged in time for his hobbies which were photography, stamp collecting, and horticulture. He was most proud of his peony development and his entries won many show awards in national and local competition. In 1952 he was Chairman of the International Peony Show which was held in Kansas City.

The following editorial appeared in the Kansas City Star after his death:

DR. MANTZ'S HUMAN SERVICE

In the gaining battle against tuberculosis probably no physician has had a more active part than Dr. Herbert L. Mantz. Until his death yesterday he carried a tremendous load of public service work in addition to his own heavy practice.

During and after his presidency of the National Tu became well known to the specialists of many countri ings in England, Italy, France, Norway, and Swede on the kind of efforts that have given the United S losis rate in the world.

His death followed by two days his return from Panama City where he served as a delegate to the Ce Against Tuberculosis. It was his fourth such meeting

As national consultant on tuberculosis for the Ve traveled the country visiting hospitals and confer Friends report that Veterans Administration work a of his average month.

To Dr. Mantz national leadership simply widened to serve humankind. He contributed his prominent tuberculosis that is now saving many thousands of li

FLORENCE

THE

TO THIS VOLUME H

FROM THIS POSITIO

THE BEGINNING O

THE CONVENIENCE

MEDICAL SERVICE BUREAU

POSITIONS WANTED

Experienced chest specialist and administrator with outstanding qualifications desires medical directorship or superintendency. Graduate of Class A American medical school. Excellent references from chest specialists of national repute. Please address all inquiries to Box 284B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Thoracic surgeon, completing training July 1, 1954, desires part-time appointment in institutional work with opportunity to develop private practice. Would also consider association with medical group or busy surgeon. Ten years experience in general practice, three years general surgery res-

surgery
vascular
oscopist.
to Box
st Phys-
Chicago

E INDEX

E HAS BEEN REMOVED

TION AND PLACED AT

OF THE FILM FOR

CE OF READERS.

Resi-
pproved
ry and
d Hos-
main-
eligible
all in-
College
hestnut

sidency
4; em-
y, bac-
emistry
Write

Clinical Director, Trudeau Sanatorium, Trudeau, New York.

The Veterans Administration Hospital, Downey, Illinois, has several vacancies for physicians in the 297-bed Tuberculosis Unit of the hospital. Salaries are determined by experience and qualifications. Salary range for physicians in Department of Medicine and Surgery is from $5,500 per annum to $9,600 per annum with a maximum, after periodical promotions, of $10,600 per annum. Applicants must be between ages of 21 and 54, hold degree of Doctor of Medicine from an approved school, and must have completed an approved internship, as well as posess a license to practice medicine in a state or territory of the United States and must meet physical qualification standards. Must also be citizen of the United States. Applicants should write to the Manager, VA Hospital, Downey, Illinois. Hospital is located approximately 35 miles north of Chicago near Waukegan, Illinois.

Florida Opportunities For Qualified Physicians

Staff Positions for Both Junior and Senior Physicians in Four Modern Tuberculosis Hospitals.

Modern Antibiotic and Drug Therapy employed together with advanced techniques in chest surgery.

The Southeast Florida Tuberculosis Hospital

BEGINNING SALARIES

Junior Physician - - -	**$6,600**
Senior Physician - - -	**7,800**

PLUS Furnished Home or Equal allowance.
PLUS Earned Retirement after Ten Years of Service.

License in any one state acceptable for two years.

If you are interested in one of the following specific locations please write directly to the Medical Director for additional information:

Benjamin L. Brock, M.D., Medical Director
Central Florida Tuberculosis Hospital
P. O. Box 3513, Orlando, Florida.

Alfred M. Dietrich, Jr., M.D., Medical Director
Southwest Florida Tuberculosis Hospital
4000 West Kentucky Ave., Tampa 7, Florida

L. C. Manni, M.D., Medical Director
W. T. Edwards Hospital
2323 Phillips Road, Tallahassee, Florida.

William L. Potts, M.D., Medical Director
Southeast Florida Tuberculosis Hospital
P. O. Box 1411
Lantana, Florida (Near West Palm Beach).

Henry C. Sweany, M.D., Chief Medical Director
State Tuberculosis Board
4000 West Kentucky Ave., Tampa 7, Florida.

ENJOY YOUR WORK AND PLAY IN THE NATION'S BEST CLIMATE

interests. He was a member of the Kansas City University Club. He was, for many years, a deacon of the First Baptist Church and on the Board of Trustees, active in the Fund Raising Campaign for the Baptist Memorial Hospital.

Throughout his entire medical life, he wedged in time for his hobbies which were photography, stamp collecting, and horticulture. He was most proud of his peony development and his entries won many show awards in national and local competition. In 1952 he was Chairman of the International Peony Show which was held in Kansas City.

The following editorial appeared in the Kansas City Star after his death:

DR. MANTZ'S HUMAN SERVICE

In the gaining battle against tuberculosis probably no physician has had a more active part than Dr. Herbert L. Mantz. Until his death yesterday he carried a tremendous load of public service work in addition to his own heavy practice.

During and after his presidency of the National Tuberculosis Association he became well known to the specialists of many countries. To professional meetings in England, Italy, France, Norway, and Sweden he carried information on the kind of efforts that have given the United States the lowest tuberculosis rate in the world.

His death followed by two days his return from Caracas, Venezuela, and Panama City where he served as a delegate to the Central American Congress Against Tuberculosis. It was his fourth such meeting in Latin America.

As national consultant on tuberculosis for the Veterans Administration he traveled the country visiting hospitals and conferring on their problems. Friends report that Veterans Administration work alone took about 10 days of his average month.

To Dr. Mantz national leadership simply widened the physicians obligation to serve humankind. He contributed his prominent part to a fight against tuberculosis that is now saving many thousands of lives each year.

FLORENCE E. MacINNIS, M.D.

MEDICAL SERVICE BUREAU

POSITIONS WANTED

Experienced chest specialist and administrator with outstanding qualifications desires medical directorship or superintendency. Graduate of Class A American medical school. Excellent references from chest specialists of national repute. Please address all inquiries to Box 284B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Thoracic surgeon, completing training July 1, 1954, desires part-time appointment in institutional work with opportunity to develop private practice. Would also consider association with medical group or busy surgeon. Ten years experience in general practice, three years general surgery residency, two years thoracic surgery residency including cardiovascular training; competent bronchoscopist. Please address all inquiries to Box 285B, American College of Chest Physicians, 112 E. Chestnut Street, Chicago 11, Illinois.

POSITIONS AVAILABLE

Thoracic surgery resident: Residency available July 1, 1954, approved by Board of Thoracic Surgery and Council Medical Education and Hospitals. $350 per month, plus maintenance. Require U.S.A. citizen, eligible Ohio license. Please address all inquiries to Box 279A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Six to twelve months residency available starting July 1, 1954; emphasis on physiology, radiology, bacteriology, pathology and biochemistry as well as clinical practice. Write Clinical Director, Trudeau Sanatorium, Trudeau, New York.

The Veterans Administration Hospital, Downey, Illinois, has several vacancies for physicians in the 297-bed Tuberculosis Unit of the hospital. Salaries are determined by experience and qualifications. Salary range for physicians in Department of Medicine and Surgery is from $5,500 per annum to $9,600 per annum with a maximum, after periodical promotions, of $10,600 per annum. Applicants must be between ages of 21 and 54, hold degree of Doctor of Medicine from an approved school, and must have completed an approved internship, as well as posess a license to practice medicine in a state or territory of the United States and must meet physical qualification standards. Must also be citizen of the United States. Applicants should write to the Manager, VA Hospital, Downey, Illinois. Hospital is located approximately 35 miles north of Chicago near Waukegan, Illinois.

Florida Opportunities For Qualified Physicians

Staff Positions for Both Junior and Senior Physicians in Four Modern Tuberculosis Hospitals.

Modern Antibiotic and Drug Therapy employed together with advanced techniques in chest surgery.

The Southeast Florida Tuberculosis Hospital

BEGINNING SALARIES

Junior Physician - - -	**$6,600**
Senior Physician - - -	**7,800**

PLUS Furnished Home or Equal allowance.
PLUS Earned Retirement after Ten Years of Service.

License in any one state acceptable for two years.

If you are interested in one of the following specific locations please write directly to the Medical Director for additional information:

Benjamin L. Brock, M.D., Medical Director
Central Florida Tuberculosis Hospital
P. O. Box 3513, Orlando, Florida.

Alfred M. Dietrich, Jr., M.D., Medical Director
Southwest Florida Tuberculosis Hospital
4000 West Kentucky Ave., Tampa 7, Florida

L. C. Manni, M.D., Medical Director
W. T. Edwards Hospital
2323 Phillips Road, Tallahassee, Florida.

William L. Potts, M.D., Medical Director
Southeast Florida Tuberculosis Hospital
P. O. Box 1411
Lantana, Florida (Near West Palm Beach).

Henry C. Sweany, M.D., Chief Medical Director
State Tuberculosis Board
4000 West Kentucky Ave., Tampa 7, Florida.

ENJOY YOUR WORK AND PLAY IN THE NATION'S BEST CLIMATE

Friedman Diagnostic Clinic

Complete Diagnostic Service

Internal Medicine — Diseases of the Chest — Pneumoconioses

1906 Ninth Avenue South Phone 54-3324 Birmingham, Alabama

CALENDAR OF EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

20th Annual Meeting, American College of Chest Physicians
Fairmont Hotel, San Francisco, June 17-20, 1954.

Third International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Barcelona, Spain, October 4-8, 1954.

Interim Session, American College of Chest Physicians
Delano Hotel, Miami Beach, Florida, November 28-29, 1954.

POSTGRADUATE COURSES

9th Annual Postgraduate Course on Diseases of the Chest
Hotel Knickerbocker, Chicago, Illinois, October 18-22, 1954.

7th Annual Postgraduate Course on Diseases of the Chest
Hotel New Yorker, New York City, November 8-12, 1954.

8th Annual Postgraduate Course on Diseases of the Chest
Bellevue-Stratford Hotel, Philadelphia, Pennsylvania, Spring, 1955.

ALUM ROCK SANATORIUM

SAN JOSE, CALIFORNIA

TELEPHONE CLAYBURN 8-4921

A Non-profit sanatorium for the treatment of tuberculosis and other diseases of the chest.

Visiting Medical Staff:

Harold Guyon Trimble, M.D., Oakland
Cabot Brown, M.D., San Francisco
J. Lloyd Eaton, M.D., Oakland
Gerald L. Crenshaw, M.D., Oakland
Glenroy N. Pierce, M.D., San Francisco
Donald F. Rowles, M.D., Oakland
James Kieran, M.D., Oakland
Robert Stone, M.D., Oakland
William B. Leftwich, M.D., Oakland

Medical Director
Buford H. Wardrip, M.D.
Telephone Clayburn 8-4921

Associate Medical Director
C. Gerald Scarborough, M.D.

100 Beds for Crippled Children ***200 Beds for Tuberculosis***

ST. JOHNS SANITARIUM, Springfield, Ill.

Complete in every detail. Rates low—because of the services of the Hospital Sisters of St. Francis.

Medical Director
DARRELL H. TRUMPE, M.D.

Address
SISTER JUDINE, R.N., Supt.

Cragmor Sanatorium

For the treatment of tuberculosis and diseases of the chest, situated near Colorado Springs in the heart of the Rockies. Ideal year-round climate. Individual apartments, with or without baths. Rates on request.

For detailed information address

HENRY W. MALY, M.D., Director
Cragmor Sanatorium
Colorado Springs, Colorado

Southern Sierras Sanatorium

• *for Tuberculosis and Allied Affections*

BANNING, CALIFORNIA

Unsurpassed year-round climate. Near but not upon the desert
Altitude 2350 feet

Freedom from Smog

90 miles east of Los Angeles on
Highways 99, 60 and 70

Sustained reputation for service and satisfaction

C. E. ATKINSON, M.D. . . *Medical Director*

FOX RIVER SANITARIUM

BATAVIA, ILLINOIS

FOR THE TREATMENT OF PULMONARY TUBERCULOSIS

Maintained by the Chicago Consumptive Aid Society — a Jewish charitable organization.

JACOB J. MENDELSOHN, M.D., *Medical Director*

For information write—

CHICAGO CONSUMPTIVE AID SOCIETY

220 S. State Street - Chicago 4, Illinois - Suite 520

MARYKNOLL SANATORIUM

MONROVIA, CALIFORNIA

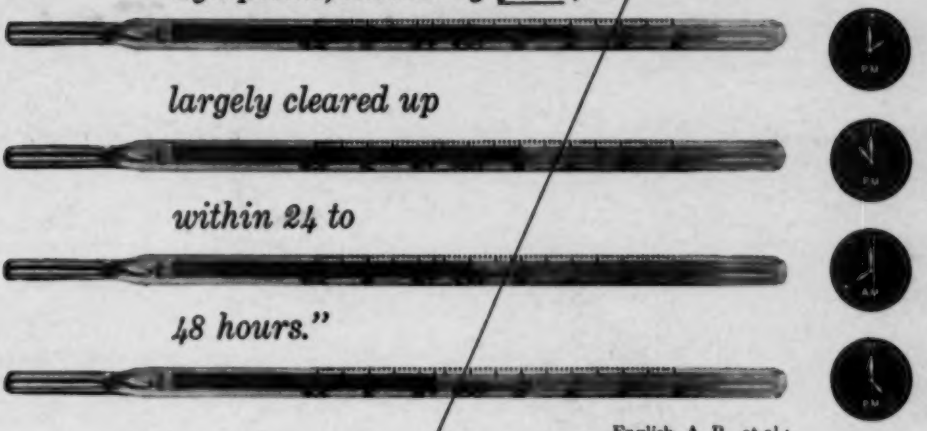
(MARYKNOLL SISTERS)

A sanatorium for the treatment of tuberculosis and other diseases of the lungs. Located in the foothills of the Sierra Madre Mountains. Southern exposure. Accommodations are private, modern and comfortable. General care of patient is conducive to mental and physical well being.

SISTER MARY PIETA, R.N.
Superintendent

E. W. HAYES, M.D.
Medical Director

"*Symptoms, including fever,*



largely cleared up within 24 to 48 hours."

English, A. R., et al.:
Antibiotics Annual (1953-1954),
New York, Medical
Encyclopedia, Inc., 1953, p. 70.

afebrile in hours c AIH **Tetracyn**

Brand of tetracycline hydrochloride

a new broad-spectrum antibiotic of unexcelled tolerance

Simple, dramatic proof of the effectiveness of Tetracyn is offered by the characteristic rapid defervescence noted in the treatment of a wide range of susceptible infectious diseases. *Think of Tetracyn* whenever you take a temperature for an AIH response in Tetracyn-sensitive infections.

Supplied: TETRACYN TABLETS *(sugar coated)*
250 mg., 100 mg. and 50 mg.

TETRACYN ORAL SUSPENSION *(amphoteric) (chocolate flavored)* Bottles of 1.5 Gm.

TETRACYN INTRAVENOUS
Vials of 250 mg. and 500 mg.

TETRACYN OINTMENT *(topical)*
30 mg./gram ointment
½ oz. and 1 oz. tubes

Roerig Rx

BASIC PHARMACEUTICALS FOR NEEDS BASIC TO MEDICINE

536 Lake Shore Drive, Chicago 11, Illinois

Each BUFFERED PARASAL-INH tablet contains 0.5 Gm. PAS and 12.5 mg. INH

Dosage Equivalents

Total Daily Tablet Intake BUFFERED PARASAL-INH		Total Daily Yield PAS	+	Isoniazid
24 Tablets	=	12 Gm.	+	300 mg.
20 Tablets	=	10 Gm.	+	250 mg.
18 Tablets	=	9 Gm.	+	225 mg.
16 Tablets	=	8 Gm.	+	200 mg.

℞ *Ideal dosage form for OPD and domiciliary treatment*

SINGLE DOSAGE FORM ASSURES INTAKE OF BOTH PAS AND INH

EFFECTIVE because combination BUFFERED PARASAL-INH therapy both diminishes and postpones development of resistance.

ECONOMICAL and ***CONVENIENT*** because 40% FEWER TABLETS are required. 17 BUFFERED PARASAL-INH tablets replace 28¼ tablets (24 tablets sodium PAS 0.5 Gm. plus 4¼ tablets INH 50 mg.).

WELL TOLERATED because UNIQUE BUFFER incorporated in each tablet virtually prevents GI upset even in cases intolerant to ordinary sodium PAS and INH taken separately. Sodium and sugar free.

Write for samples, literature, complete information

THE Panray CORP.

340 CANAL STREET, N.Y. 13, N.Y.

Copyright 1954: The Panray Corp., New York

See You at Booth No. 24 in San Francisco